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## THE TREATMENT OF ALCOHOLICS IN A DANISH PROVINCIAL TOWN

By MALTHE JACOBSEN

Aalborg is a provincial town in Denmark with a little over 100,000 inhabitants. It has a port and several industrial plants, a wharf, a cement factory, a brewery, etc.; moreover, it is the main seat for the Danish liquor industry.

In September, 1950, a *Committee on Alcoholism* was founded here with the sole object to run an outpatient clinic. It has been in work since then, and in the following the organization and the results obtained will be described.

The members of the committee are officials from the church, the city authorities, the most important industries, the Trade Unions, and a few other organizations. These official representatives from public life act not only as a guarantee towards the public, but are also active in the efforts to resocialize the patients. The importance of having representatives in key positions within almost all branches does not need to be emphasized. The Public Health Officer of the county acts as a chairman of the committee. The daily work of the clinic is supervised by a smaller working subcommittee consisting of 5 members under the chairmanship of the Public Health Officer. The Committee is concerned only with the treatment and resocialisation of alcoholics; it exerts no other functions such as general educational work, public information about alcohol and alcoholism, etc.

The treatment has so far only been ambulatory through a clinic in which the patients receive medical treatment, advice on social and family troubles and a general mental-hygienic treatment.

The clinic is open daily in the morning and during the evening after working hours. The daily work in the clinic is conducted by a social worker who also acts as a secretary for the working committee. Newcomers are first seen by

him. Their social background, economic and social problems are recorded, and provisional steps are taken to get the patients into treatment. The patients are next seen by one of the 3 doctors connected with the clinic, each of them being on duty one evening a week, and the treatment of possible somatic diseases in connection with their alcoholism is started. The cases are then discussed in the subcommittee. The secretary helps the patients to solve their most urgent social problems. Cash is never given to the patients, but arrangements are made with their creditors. In case they are unemployed it has often been possible to get them employment, and especially on this point the wide-spread relations of the committee plays an important role. Disulfiram (in the form of Antabuse) is always given. The patients are seen frequently in the clinic. About 30—60 patients are coming daily in order to receive the dose of disulfiram necessary to keep them sober.

During the treatment the patients are constantly supervised by the secretary. He keeps in personal contact with the patients so that he can be able to stop threatening relapses. Moreover, he tries to get the patients into the local *Alcoholics Anonymous* group (here named "Ring i Ring"). This group was founded by the clinic with the aim to reinforce the psychic resistance of the patients build up by the clinic. It has about 60 members who meet once a week at a social gathering with lectures, various entertainments, etc. The wives of the patients generally take part in these meetings. Direct psychiatric treatment including organized group therapy has not yet been employed.

The patients are not charged for the treatment. The committee pays the rent of the premises and the secretary's fee. The rest of the committee including the 3 doctors have so far worked without any financial compensation.

## MATERIAL AND RESULTS

In order to get a proper observation time the material considered here consists only of patients seen in the clinic from September 15, 1950, until December 31, 1952, and their status as of February 15, 1954, is given. This makes an observation time from 13 months up to 3½ years. During the period mentioned 308 patients were seen; of these only seven are women, who shall be mentioned separately in the following. Of the total material of 301 men the following 35 are not taken into consideration: 21 who have moved from the town, five who came to the clinic without being alcoholics, four who were considered unfit for the treatment in the clinic after psychiatric examination, and five who died. In none of these cases had the cause of death any connection with the treatment or direct relation to the alcoholism.

The remaining 266 male patients will be considered from a sociological and criminological point of view, and attempts will be made to classify the patients psychiatrically. The patients are evaluated in respect to their attitudes towards alcohol and the degree of resocialisation. In cases of doubt the patient in question has always been classified in the lower group.

As mentioned above, none of the deaths can be attributed to the disulfiram medication. In two cases a psychotic reaction occurred during the treatment; both patients had previously been hospitalized with psychoses.

In the classification of the results the patients are grouped according to the following criteria:

++++: no or «normal» use of alcohol. In cases of social insufficiency at the beginning of the treatment, complete resocialisation is required.

+++ : A few relapses. Contact with the clinic is not necessary. In cases of social insufficiency at the beginning of the treatment, complete resocialisation is required.

++ : Occasional relapses. Contact with the clinic in the case of a relapse is considered necessary in this group. In cases of social insufficiency at the beginning of the treatment, complete or considerable resocialisation is required.

+ : Frequent relapses. Constant contact with the clinic is required. Unstable resocialisation.

o: Nothing noticeable is obtained, perhaps a transient improvement.

With "relapse" is understood an alcohol consumption resulting in an (undesired) intoxication (loss of control over the intake) of a duration of one or several days. With "normal consumption" is here understood complete control over the alcohol intake, in some cases by means of disulfiram intake the day after rare, occasional "deliberate" intoxications (on special occasions, when the individual really has had the intention

of "Going on a binge" and beforehand has prepared a disulfiram intake the following morning).

Table 1.  
Results of treatment according to age.

	Total	+	+	+	+	o
		+	+	+	+	o
< 24 years	14	1	4	7	0	2
25—29 years	52	7	19	9	6	11
30—39 years	89	14	28	24	6	17
40—49 years	71	18	25	6	9	13
> 50 years	40	18	7	4	3	8
Total . . . . .	266	58	83	50	24	51
% . . . . .	100	21.8	31.2	18.8	9.0	19.2

Table 1 shows the results according to the age groups. It is seen that satisfactory results have been obtained in 53 per cent of all cases (the groups + + + + and + + +). Moreover, 18.8 per cent show fair results (group + +). In particular, the patients in this latter group indicate the necessity of having a firm organization and an effective clinic with social, psychological and medical facilities plus connections in an A. A. group. Many patients in this group frequent the clinic daily during long periods in order to receive their disulfiram dose.

The two last groups (+ and o) represent the poor results, but nevertheless the patients of these groups often require a good deal of work. It is against the policy to refuse to help when they repeatedly apply for help, in spite of our experience that our efforts more or less are in vain. However, some of these patients have transgressed the limits of our patience.

Table 2.  
The results of treatment according to domestic and marital status.

	Total	+	+	+	+	o
		+	+	+	+	o
<b>Married.</b>						
Good living quarters	145	46	44	27	8	20
Poor > >	33	1	14	7	5	6
No > >	9	0	7	1	1	0
<b>Single.</b>						
Separated . . . . .	15	1	3	4	2	5
Divorced . . . . .	18	2	4	2	4	6
Widowers . . . . .	7	2	1	1	1	2
Unmarried . . . . .	39	6	10	8	3	12
Total . . . . .	266	58	83	50	24	51

Table 2 shows the grouping according to domestic and marital status. It is surprising that not less than 20 patients in the group o still are living in good living quarters (with which is understood living quarters of a good or fair hygienic standard and of an appropriate size in re-

lation to the number of inhabitants). Even after subtraction of the 12 patients who are fully or partially employed as a result of the treatment (Groups A and B in Table 5), 8 patients remain whose social position has been considerably reduced, but who still live under good or fairly good conditions. This fact is to be considered on the background of the social policy in Denmark according to which wives and children are supported, e. g., with help to the rent even if the husband is an alcoholic. Moreover, many of the wives of alcoholics are able and energetic women who are employed and keep their homes together in this way.

Table 3.  
Results of treatment according to the social conditions of the patients' childhood.

	Total	++	+	+	+	0
Broken homes without load .....	17	1	7	2	2	5
Broken homes with load .....	33	0	7	5	4	17
Unbroken homes without load .....	97	54	63	40	15	25
Unbroken homes with load .....	19	3	6	3	3	4
Total .....	266	58	83	50	24	51

In Table 3 the results are grouped according to the social conditions of the patients' childhood. With "broken homes" is here understood homes where one of the parents or both were missing during the childhood of the patient. Both groups are divided in the subgroup "with or without social or criminal load" which means that the home has been under supervision by some public authority and/or that one of (or both) parents have been criminals.

Table 4.  
Results of treatment in patients with previous sentences.

	Total	++	+	+	+	0	criminal relapses
1—2 sentences ..	52	6	18	6	7	15	0
Several sentences	23	2	1	6	2	12	15
Total .....	75	8	19	12	9	27	15

Table 4 shows the grouping according to earlier criminality of the patients. The terms "1—2 sentences" or "several sentences" applies to the state of the patients at the time they reported to the clinic. As in all other tables, the results refer both to the patients' attitude towards alcohol and their degree of resocialisation during the treatment. It is probably not without connection with the treatment that no patients with 1—2 sentences

have had criminal relapses. The clinic has worked as a control institution for 20 persons who had been sentenced on probation or released on parole under condition that they submitted themselves to a treatment for alcoholism. The sentence was made effective in 1 of 13 patients sentenced on probation and in 3 of 7 patients released on parole because they did not submit themselves effectively to the treatment. In spite of the short observation time, these results seem to justify a certain optimism as to the effect of the results, especially among young first offenders.

Table 5.  
Results of treatment according to the working conditions of the patients at the beginning of the treatment.

	Total	++	+	+	+	0
A. normally employed, no previous difficulties .....	72	27	23	13	3	6
B. previously normally employed, now unemployed .....	86	18	35	22	5	6
C. unemployed during a long period .....	108	13	25	15	16	39
Total .....	266	58	83	50	24	51

In Table 5 the patients are classified according to their working conditions at the beginning of the treatment. The results given in Group A (fully employed at the beginning of the treatment) are based only on the patients' attitude towards alcohol. For this reason the patients of this type placed in the groups ++, +, and 0 have not necessarily shown a social decline during the observation time, although such can be foreseen within a limited time.

The results obtained with the patients within Group C show clearly the economical significance of the work with this kind of patient who already during a longer time has been a load to the public. 35 per cent of this group has been fully resocialized and employed. Moreover, 14 per cent of the same group are completely or almost completely resocialized. However, continuous supervision and help from the clinic is required in order to maintain this status among such patients, and it is not astonishing that most of the failures are found in this group.

Among the total number of 51 failures are found types of patients who presumably under all circumstances were hopeless to treat ambulant.

These 51 patients can be grouped as follows:

- 21 patients of the "skid row" type.
- 12 psychopaths, some of them criminals.
- 11 showing lack of energy and ambition.
- 3 periodically psychotic or narcomans (with several admissions to psychiatric clinics).
- 4 lacking persistence to receive proper treatment.

If it has been possible to hospitalize some of these patients, better results could presumably have been obtained in some of the cases, especially those of the "skid row" type.

Four of the seven female patients were prostitutes. In none of these 4 cases a result has been obtained. The remaining 3 have no longer any problem with alcohol and their personal and family problems have been settled.

#### DISCUSSION

The work in Aalborg is characterized by two facts: the partly improvised working conditions and the use of Antabuse. As already emphasized, no specialists are employed: the social worker is a man with common social understanding and a burning interest for this special problem, and none of the doctors are psychiatrists. It has also been emphasized that the clinic is run exclusively on an outpatient basis. In the first place, we do not dispose over sufficient personnel, and secondly it has been economically impossible for us to establish the working-home which we consider essential for an effective treatment of the more difficult cases.

We insist that the patients who seek our help must take disulfiram. It is our experience that a regular intake of disulfiram, forcing the patient to remain abstinent, is an excellent adjuvant during the special treatment. Moreover, we have got the impression that this drug acts as a proper therapeutical remedy in the sense that the craving for alcohol is reduced during the prolonged disulfiram induced abstinence. The period in which the patients need to take disulfiram varies considerably, naturally depending on the result of the other treatment. Some of our patients have taken disulfiram during 3 years and are still

taking it. Others take disulfiram in periods when they feel they need support. Still others have taken disulfiram during one or two years and now remain sober without. One patient, a severe alcoholic, took disulfiram for 2 weeks only, and has now during 2 years touched neither alcohol nor disulfiram.

Apart from the human significance of our work, it obviously has a great economical significance for a community like the Danish which has legal obligation to support its citizens, the alcoholics and their families included.

It shall finally be emphasized that the work of the clinic in Aalborg has been of great significance for changing the attitude of the public opinion towards alcoholics. We have obtained a situation where workers being normal alcohol consumers spontaneously advise their mates to seek our assistance in case they show signs of a beginning addiction. One consequence of this fact is that the patients who have sought us during the last year generally are less heavily alcoholized compared with the patients during the first years.

#### SUMMARY

The paper gives a survey of the results of the organized treatment of alcoholism in a Danish provincial town of 100,000 inhabitants. During the period September 15, 1950, to December 31, 1952, 266 men and 7 women have been submitted to treatment and have been observed from 1 to 3½ years. The clinic is only ambulatory and is run by doctors and a social adviser. The treatment is social and psychological under the cover of disulfiram (Antabuse). Later the clinical treatment is continued in an Alcoholics Anonymous Club, which works under the supervision of the organization.

## THE ANTABUS-ALCOHOL REACTION

### SUMMARY OF CLINICAL AND EXPERIMENTAL INVESTIGATIONS

By KNUD RABY

In the course of time, alcohol addiction has been subject to many and often drastic measures. After a number of epoch-making studies by Hald, Jacobsen and co-workers in 1948, considerable progress has been made in this field with the introduction of Antabus (tetraethylthiuram disulphide — disulfiram) into the medical counteraction of this social problem.

To support the practical work thus started, experimental investigations were required in order to increase our knowledge of the mode of action of Antabus.

Tetraethylthiuram disulphide is a well-defined substance, first produced in 1881 in the form of a white or faintly yellowish powder of a slightly bitter taste. It is only slightly soluble in water, but the resorption from the intestinal canal is fairly easily effected; the substance is then distributed in the organism in such a manner that the highest concentration is present in the adrenal glands and in the spleen, whereas the liver and the blood contain decreasing concentrations. Elimination is slow, going on for days.

The toxicity was examined by Hanzlik &



Irvin (12), who found that the lethal dose was about 3 gm per kg body weight in the case of rabbits and pups; this corresponds to about 180 g in the case of human beings weighing 60 kg.

In man the effect of therapeutical doses (without alcohol) consists in slight malaise in the form of fatigue, sleepiness, constipation or diarrhoea, headache and dizziness. It has also been stated that it exerts a sedative effect; but psychoses have been described (4, 8, 21, 28). The discomfort subsides in spite of continued treatment; in the case of psychoses, however, administration must be discontinued. A supposed diabetogenic effect could not be demonstrated in experiments performed by Lauritzen & Raby (20), and the fear of hepatic lesions is apparently also unfounded (13, 16). But Antabus inhibits the aldehyde oxidases of the liver (Kjeldgaard (18) and others), thus causing accumulation of these substances in the organism (Jacobsen & Larsen (15)). This effect must be considered as of special importance to the reaction produced by Antabus and alcohol.

The purpose of the investigations mentioned in the following was to attempt an elucidation of the mechanism of this reaction and to procure a broad idea of its course and of possible variations (32).

The effect of alcohol alone and that seen after pretreatment with Antabus were examined in a number of experiments on voluntary subjects, either alcohol addicts or persons with little or no consumption of alcohol. Experiments with acetaldehyde infusion proved to be very painful, and had to be abandoned.

It was attempted to elucidate the following three main questions:

(1) What is the clinical course of the reaction, and which variations may be expected?

(2) What are the changes in organs and blood that can normally be expected in connection with this reaction?

(3) Is it possible to say anything about the relationship between the degree and course of the reaction on the one hand and the two substances, Antabus and alcohol, on the other hand?

The result of the investigations was that the intake of alcohol alone, even in large doses, does not elicit clinical reaction as in the case of treatment with Antabus; one case with "spontaneous" reaction forms an exception, and has been previously described (25).

After treatment with Antabus the intake of alcohol elicits in most cases a symptom complex of typical nature and course as previously described (9, 16, 33, 5, 27). Characteristic signs are flushing of the face, which sets on very soon, acetaldehyde odour in the respiratory air, tachycardia, headache, and, in some cases, a dry cough. Later, fatigue and often nausea and vomiting occur, associated with pallor and perspiration. A fall in the blood pressure is seen in almost all

cases; collapse occurs in a few. Hyperaesthesia has also been noticed during the course of the reaction, but never after the intake of alcohol alone. Finally, mention may be made of colicky abdominal pain and paraesthesiae in the hands and feet. The cause of these complaints is not clear, but the clinical picture bears some resemblance to that described by other authors in cases with changes in the potassium level of the blood of varying causation. As similar changes in the potassium content of the blood have been demonstrated during the Antabus-alcohol reaction (Raby (26)), it is theoretically possible that these may be contributory to the appearance of these symptoms.

Fatal cases in conjunction with the reaction have been previously reported (3, 17). A thorough analysis of these was made and described in detail by Jacobsen (14); it appeared from this that the risk did not consist in treatment with Antabus, but was present only when this was taken with alcohol, and that similar cases might occur after the intake of large quantities of alcohol alone. The risk in treatment with Antabus properly performed must therefore be considered very slight; it should also be borne in mind that the risk incurred by alcohol addicts is very considerable in itself.

As a rule, the reaction is concluded by the patient's falling calmly asleep, waking after 1 or 2 hours in complete well-being.

According to the investigations performed, the degree of the reaction apparently increases with rising doses of Antabus. No interdependence was found between the acetaldehyde concentration of the blood, or the rate at which this reached maximum, and the degree of the reaction.

With regard to the presence of acetaldehyde in the organism, it is stated that it is normally present in small quantities in the blood. Following the intake of alcohol the acetaldehyde level rises in the blood, and after intravenous infusion of alcohol in animals Larsen (19) found that the acetaldehyde-formation depends on the alcohol concentration in the blood.

In investigations on resting human subjects, Raby (29) also found a rising acetaldehyde level in the blood, dependent on the alcohol concentration. The maximal values found varied from 0,590 mg per 100 ml to 1,700 mg per 100 ml, averaging 1,037 mg per 100 ml. After preceding treatment with Antabus a more rapid rise and higher maximal acetaldehyde levels were found in the blood, varying from 0,640 mg per 100 ml to 2,510 mg per 100 ml, averaging 1,335 mg per 100 ml. There is apparently a relation between the dose of Antabus administered and the acetaldehyde level in the blood. This is in accord with previous investigations by Hald, Jacobsen & Larsen (10).

That acetaldehyde is produced in the liver can be considered a fact. According to experiments

performed by Jacobsen & Larsen (15), the increased proportion of acetaldehyde in the blood after the intake of Antabus and alcohol can be satisfactorily explained by the action of Antabus on the acetaldehyde metabolism (inhibition of aldehyde oxidase).

The action of acetaldehyde in the organism has been previously described by Handovsky (11) & Nelson (22); they found stimulation of the respiration, a rise in the blood pressure, and tachycardia. Christensen (7) showed that acetaldehyde causes a rise in the blood pressure followed by a fall, and that Antabus prolongs the latter effect. Finally, investigations by Asmussen, Hald & Larsen (2) showed that acetaldehyde can release the symptoms characteristic of the Antabus-alcohol reaction.

Respiration is influenced during the reaction: this manifests itself by subjective dyspnoea. This effect is due to acetaldehyde, and is exerted via the chemoreceptors in the carotid sinus (1).

With subjects under the influence of alcohol alone, Raby (30) found a varying effect on respiration in the form of a reduction as low as 18 per cent or a rise up to 22 per cent of the normal values at rest. No relation was found between these changes and the alcohol concentration, and the ventilation in the experiments was quite independent of the acetaldehyde level in the blood.

After the intake of Antabus and alcohol all cases showed a rise in ventilation up to 108 per cent, averaging about 50 per cent of values at rest, and increasing with rising acetaldehyde level in the blood. During the hyperventilation the  $\text{CO}_2$  content in the alveolar air was lowered. Inhalation of pure oxygen exerted a considerable effect on the increased ventilation, as it was reduced by 27 per cent on the average. However, no definite influence on the subjective condition could be demonstrated.

The reaction of the blood, measured with a glass electrode (Raby (31)) at 37° C. with the subject at rest, averaged for arterial blood pH 7.445 as normal value, with variations from 7.401 to 7.480. In all experiments the intake of alcohol caused a change in pH in an acid direction, increasing with rising alcohol concentration in the blood. In such experiments, pH varied from 7.369 to 7.424, averaging 7.405.

However, when alcohol is taken after preceding treatment with Antabus, the reaction of the blood always shows a change in an alkaline direction, with pH values from 7.464 to 7.600, averaging 7.505. A distinct tendency to rising pH with increasing concentration of acetaldehyde in the blood was found, but the changes were apparently also to some degree dependent on the dose of Antabus administered.

The cause of alkalosis in these experiments must be a decrease of  $\text{CO}_2$  in the blood owing to

hyperventilation caused by the increased acetaldehyde content in the blood.

But also after the intake of alcohol alone it was found that the alkali reserve of the blood was reduced and almost to the same degree. It would be impossible to say anything about the reaction of the blood solely by determining its  $\text{CO}_2$  content. It is therefore important to bear in mind that an alkalosis with lowered bicarbonate values in the blood is present during the Antabus-alcohol reaction.

The effect on the organs of circulation is very conspicuous during the Antabus-alcohol reaction. Immediately at the beginning of the reaction there is often considerable tachycardia, and changes in the blood pressure are observed almost simultaneously. A slight rise followed by a considerable fall is characteristic. The diastolic blood pressure often falls to zero, and the systolic pressure may fall to 50 mm Hg. In some cases this great fall was associated with collapse and irregular action of the heart.

In the great majority of cases the reaction was accompanied by electrocardiographic changes (28). These are typical, and can be divided into two groups: (a) flattening of T waves only (type +), and (b) flattening of T waves and depression of the S-T segment (type ++). The two types were equally frequent, occurring from 5 to about 90 minutes after intake of alcohol and persisting for 65 minutes to about 4 hours; in one experiment, however, it was demonstrated after 24 hour (Raby (28)). The changes are thus transitory, and it has been supposed that they are caused by ischaemia in the musculature of the heart, or by the tachycardia (6, 23). This assumption could not be confirmed by my experiments; the conclusion from these was that during the Antabus-alcohol reaction the organism is exposed to a great number of changes occurring almost simultaneously. In the course of the reaction two types of electrocardiographic changes occur; broadly speaking, one (type +) is seen in the case of less pronounced changes, whereas type ++ accompanies the more pronounced changes in the organism. It was impossible to demonstrate a definite relation to any single change, except for the variations in the potassium level of the blood and the dose of Antabus administered.

Investigations on the potassium content in the blood (Raby (26)) with subjects at rest showed slight displacements in arterial and venous blood within the limits of the normal. Hyperventilation caused no appreciable changes here, whereas a considerable fall in the serum potassium level was found after intake of alcohol in one case.

In experiments with Antabus and alcohol, however, changes were found in the serum potassium level, apparently in relation to the acetaldehyde concentration in the blood. The greatest variations were found in arterial blood in the form of a fall

in the potassium level, but considerably varying both in degree and with regard to the rate at which they passed off. In many cases they also differed from the changes in venous blood.

It was noticed that the electrocardiographic changes became more pronounced (type ++ ) with increasing changes in the potassium level in arterial blood; the electrocardiographic findings were of the same type as previously described by other authors in conjunction with hypopotassaemia. As previously mentioned, no other convincing relation was demonstrated between the electrocardiographic changes and other simultaneous variations in the course of the Antabus-alcohol reaction; therefore it was apparently permissible to conclude that there was a connection between the variations in the potassium level of the blood and the electrocardiographic changes.

The question of the importance of acetaldehyde to the Antabus-alcohol reaction is very difficult to answer definitely. Asmussen, Hald & Larsen (2) have shown that acetaldehyde can release the symptoms characteristic of this reaction, and, as already mentioned, it is well established that the intake of alcohol after preceding treatment with Antabus increases the acetaldehyde concentration in the blood. Various authors consider that a distinction can be made between the effect of acetaldehyde and that of Antabus, but this has not been definitely confirmed. That the question is not quite simple, appears from the fact that acetaldehyde, even in quite considerable concentrations, does not always produce a reaction, such as is seen, for instance, after the intake of alcohol alone and in a few experiments with preceding treatment with Antabus (Raby (27)). In this connection the possibility of the presence of acetaldehyde in a non-active state has been ventilated, but never confirmed. It seems, however, to appear from my experiments that the acetaldehyde concentration in the blood is hardly solely decisive to the degree of clinical reaction, but that the latter is also in close relation to the dose of Antabus administered.

The total conclusion must be that the Antabus-alcohol reaction must presumably be considered the outcome of an interference with several of the normal, intermediary metabolic processes in the organism, only some of which are known. The most essential factor is undoubtedly the accumulation of acetaldehyde caused by the inhibition of its conversion in the presence of Antabus. It must be considered probable that acetaldehyde is responsible for the most essential symptoms in the course of the Antabus-alcohol reaction, although Antabus apparently contributes in a manner yet unknown to the course and degree of the reaction.

Antabus should never be administered in doses higher than those required to release a mild reaction.

Treatment with Antabus necessitates a thorough examination of the patient before and during the course of treatment, but must be considered safe when properly conducted.

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## REPEATED ANTENATAL CONTRA SINGLE POSTNATAL ADMINISTRATION OF VITAMIN K

### EFFECT ON PROTHROMBIN TIME OF THE NEWBORN

By HOLGER DYGGVE

In a previous publication (Dyggve, Dam & Søndergaard, 1954) we studied the influence on the prothrombin time of the newborn during the first six days of life of one single dose of Vitamin K (Synkavit or Konakion\*, Roche) given in different amounts to expectant mothers one to 48 hours before delivery. Another article (3) dealt with the influence of the sodium salt of 2-methyl-1,4-naphthoquinone bisulfite (K-vital, Leo) given a single dose of 20 or 40 mg 30 to 45 minutes ante partum.

In the present paper the influence of more than one dose of Vitamin K given during the last days of pregnancy has been investigated. In antenatally untreated newborn infants the influence of one single dose of Synkavit given immediately after birth was also studied.

We have found that a certain reduction in the incidence of haemorrhages in the newborn period can be obtained by augmenting the coagulability of the blood by the administration of vitamin K at birth (Dyggve, 1952) but this subject will not be dealt with here.

#### MATERIAL AND METHODS

Prothrombin times were determined by the method of Larsen & Plum (5). The normal prothrombin time for adults is 18–19 seconds by this method. In two series 10 and 20 mg respectively of K-vital were given on at least each of the last three days before delivery. None of these mothers or infants received any form of Vitamin K after parturition. K-vital was given as tablets containing 10 mg of the substance.

In a third series Synkavit was given within a quarter of an hour after birth to newborn infants, whose mothers had not received Vitamin K preparations during pregnancy. The newborns received 10 mg of Synkavit intramuscularly. Newborn infants weighing less than 2000 g at birth were excluded from the study.

Fig. 1 shows the distribution of prothrombin time intervals in three groups of newborn infants. The best effect on the prothrombin time was seen in Group B, where the mothers had received 20

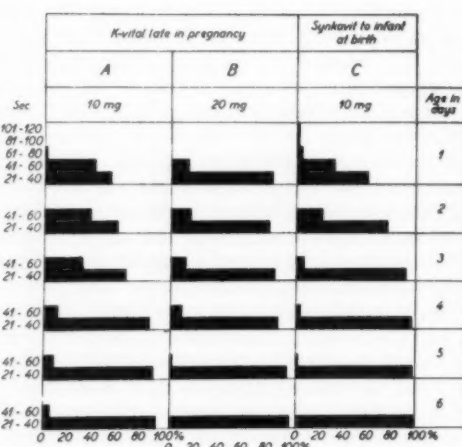


Fig. 1.

Distribution of prothrombin times of three groups of newborn infants in the first 6 days after birth. In Groups A and B the mothers were given menadione-sodium-bisulfite (K-vital, Leo) 10 and 20 mg respectively per day during at least the three last days of pregnancy. Groups A and B comprise 50 cases each. In Group C no Vitamin K was given to the mothers but the infants received 10 mg of Synkavit (Roche) intramuscularly within a quarter of an hour after birth. Group C comprises 175 infants.

Ordinate: Prothrombin time intervals (seconds).  
Abcissa: Per cent of number of cases.

mg of K-vital per day. In this group none of the infants had considerably prolonged prothrombin times during the first week of life. In Group A, where the mothers received 10 mg K-vital per day, the effect was definitely lesser than in Group B. In Group C, where the infants got Synkavit 10 mg intramuscularly at birth, 4 per cent of the infants had prothrombin times of 80 seconds or more, corresponding to a prothrombin activity lying below 10 per cent of that of normal adults. In these cases the determination of the prothrombin time had been carried out within a few hours after birth, so that Vitamin K had not had time enough to shorten the prothrombin time. From the third day up the prothrombin times were as favourable in Group C as in Group B.

From our earlier publications the distributions of the prothrombin time in groups of infants, whose mothers received a single dose of Vitamin K one to 48 hours before delivery, is shown in Fig. 2.

\* Konakion is an aqueous colloidal solution of Vitamin K<sub>1</sub>.

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When a single dose of 20 mg of K-vital, Synkavit and Konaktion was given one to 48 hours before delivery, the response (Fig. 2) was not as good as that seen in Groups A and B (Fig 1) where repeated doses of Vitamin K were given antenatally. When the single dose of K-vital, Synkavit and

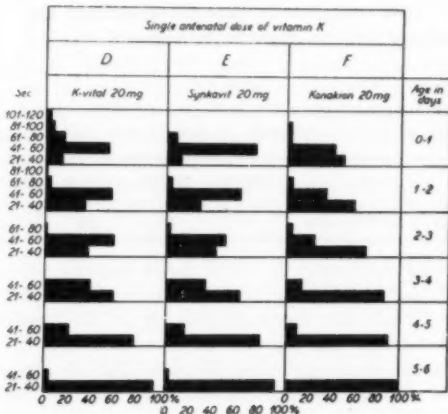


Fig. 2.

Distribution of prothrombin times in the first 6 days after birth. In Groups D and E, comprising 50 cases each, the mothers were given a single dose of 20 mg (2 tablets) of K-vital and Synkavit respectively, one to 48 hours before delivery. In Group F, comprising 100 cases, 20 mg (20 drops) of Vitamin K<sub>1</sub> (Konaktion, Roche) were given one to 48 hours ante partum.

Ordinate and abscissa as in Fig. 1.

Konaktion was 40 mg (groups of 50 cases), the response was somewhat better than that seen after 20 mg of the same preparations. The effect was, however, not as good as that obtained in

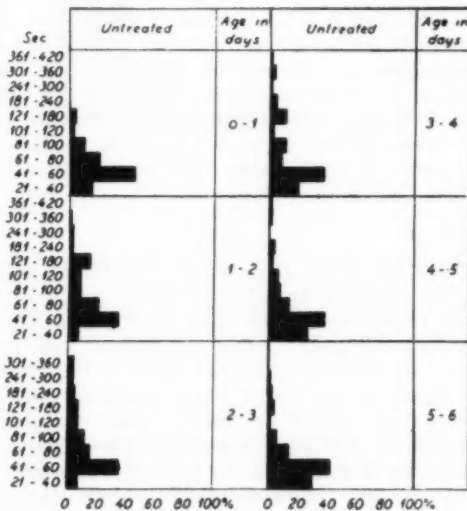


Fig. 3.

Distribution of prothrombin times of 100 untreated infants during the first 6 days after birth.

Ordinate and abscissa as in Fig. 1.

Group B (Fig. 1) where 20 mg of K-vital had been given during at least three days before birth.

The distribution of the prothrombin time in 100 untreated newborn infants is seen in Fig. 3, which shows the many cases with great prolongation around the third day of life.

The low level of prothrombin and of proconvertin (Factor VII) normally seen during the first hour after birth can often be raised by antenatal administration of Vitamin K (7).

### CONCLUSION

The best way of bringing the "prothrombin activity" during the first week of life as near to normal adult level as possible (*i. e.*, of shortening the prothrombin time) was to give 20 mg per day of Vitamin K (K-vital) during at least the last three days of pregnancy. No difference was found between cases where the mothers received the preparation for one or two weeks instead of only for three days before delivery.

### SUMMARY

The best effect on the prothrombin time during the first week of life was seen when the mothers received 20 mg per day of Vitamin K in the form of the sodium salt of 2-methyl-1,4-naphthoquinone bisulfite (K-vital, Leo) during the last three days of pregnancy. 10 mg per day of the same substance given in the same way had a less marked effect.

Even single doses of 40 mg of K-vital, Synkavit or Vitamin K<sub>1</sub> (Konaktion) given one to 48 hours before delivery did not give the response observed after repeated doses of K-vital.

Among antenatally untreated infants, who received 10 mg of Synkavit immediately after birth, 4 per cent had prothrombin levels during the first few hours of life lying below 10 % of that found in normal adults. Since this can be dangerous, antenatal and preferably repeated antenatal administration of Vitamin K in doses of 20 mg per day is recommended.

No unwanted effect was observed with this form of prophylactic treatment.

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## PROGNOSIS IN EIGHTY CASES OF MULTIPLE MYELOMA

By AAGE VIDEBAEK and HELGE JOHANSEN

Despite the variations in the individual course, the prognosis of multiple myeloma is justly regarded with pessimism. A duration of 5 years is reported to be rare (Garland & Kennedy 1948). Bayrd & Heck reported 55 patients who died of multiple myeloma. Six months after the onset less than half were surviving. The average survival time was 15 months (maximum 7 years) after the appearance of the first symptom. In 35 cases Lichtenstein & Jaffe found an average survival of about 2 years from the onset of symptoms. One patient died after 9 years and one was still alive 10 years after the onset, but these two were primarily suffering from solitary myeloma. In a series of 16 patients Laake reports an average duration of 1.8 years (ranging from 1 to 3½ years). Out of Snapper et al.'s 97 patients 64 died an average of 24 months after the appearance of the first symptom, while 8 had been ill for more than 4 years.

It must be presumed that an analysis of the number of lost working days or the number of days without pain would adequately elucidate the value of palliative treatment. These features cannot be elucidated by the present study, but since we are dealing with a disease which leads to death — generally in the course of a short time — its duration seems to be a good criterion, as a therapeutic agent of any real value must be assumed to involve an essential improvement of the prognosis *quo ad vitam*.

## MATERIAL

A total of 80 patients (48 males and 32 females) were admitted to the Radium Centre (50 patients) or to the University Hospital, Medical Department A (30 patients) during the period 1932–1955. In addition, 3 males and 2 females with solitary myeloma were admitted during the same period, but they are not included in this series of 80.

## DIAGNOSIS

The diagnosis was based on histological examination of biopsy specimens or sternal aspiration (73 patients) or merely upon the characteristic electrophoretic pattern combined with typical X-ray findings. All cases were diagnosed *in vivo* and autopsy was performed in 30. The increasing frequency with which the disease has been diagnosed (Table 1) is considered to be mainly due to improved diagnostic methods and

a growing interest in the disease. The time of diagnosis will be seen from Table 1.

Table 1.  
*Number of patients with multiple myeloma diagnosed within different intervals of time from 1930 to 1954.*

Year	1930/39	1940/44	1945/49	1950/54
Number of patients	11	19	32	23

X-ray evidence of focal bone lesions existed in 45 out of 48 patients from the Radium Centre. Nearly half the cases diagnosed in the medical department (13 out of 30) showed no X-ray signs of localized bone lesions, but in several cases diffuse decalcification. Even so, 6 of these 13 patients, who failed to show osteolytic foci, had collapse of one or more vertebral bodies. In two cases the condition was originally thought to be chronic glomerulonephritis.

## TREATMENT

Some of the patients did not receive any treatment, while most of them had brief courses of X-ray or drugs. Patients with destructive lesions, some with vertebral collapse, were given local X-ray therapy, in most cases to the lumbar column; many of these patients were also furnished with a supporting corset. For varying periods some patients received urethane, mustard gas, Haddow's compound R 48, corticotrophin, or cortisone, and a few also had a supplement of Vitamin D<sub>2</sub> and calcium phosphate. A few had a short course of stilbamidine. Blood transfusions were used to a limited extent. None of the patients were from the outset submitted to systematic or uniform treatment, so with respect to treatment this series is comparable with the majority of series published so far.

## PROGNOSIS

Three out of the five patients mentioned with solitary myeloma are alive after 4¼, 4½, and 7 years respectively; two died at the end of 6 months and 9 years. In two, the solitary myeloma was of an extraosseous localisation in the vertebral canal, giving rise to compression syndrome. One of them died of pneumonia, while the other one is alive, still without signs of generalization, more than 4 years after a non-radical excision of the tumour followed by local X-ray therapy (4000 r). These 5 patients are not included in the following prognostic considerations.

Among the 80 patients with "multiple myelomas" or more diffuse myelomatosis the mortality

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ty was considerably higher. Only 10 were alive at the conclusion of the study after 1 to 14 years' illness.

In the present paper duration denotes the period from the appearance of the first convincing signs (or, in the absence of symptoms, from the time of diagnosis) until death or conclusion of the follow-up period.

Patients whose diagnosis was based upon more special tests, performed because an elevated sedimentation rate had been discovered more or less by chance, often had no pain, anaemia, or Bence Jones proteinuria to indicate myelomatosis. Since general health control with routine determination of the E. S. R. will probably come into increasing use, the future will no doubt disclose an ever increasing number of cases with multiple myeloma still in a silent phase. Of course, the increase in duration due to such early detection must not be interpreted as an improvement in prognosis.

The average duration in the 70 deceased patients was the same for males (2 years 1 month) and females (2 years 3 months), but ranged from 2 months to 12 years. Half the deceased men and women had succumbed at the end of 1½ and 1½ years respectively.

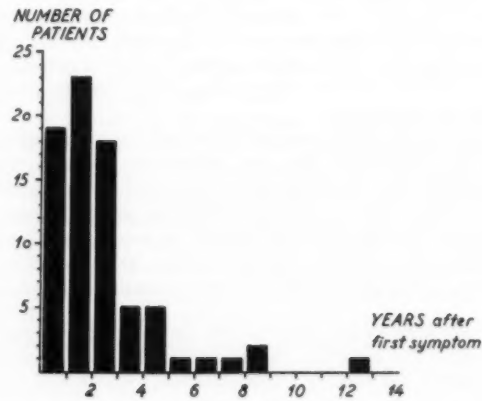


Fig. 1.

Duration of disease in 70 patients who died of myelomatosis.

As evident from Fig. 1 the disease seldom lasted for more than 2 or 3 years, although in 16 cases the duration was longer; 6 patients died after having been ill for more than 5 years. Within 2 years 60 per cent had succumbed.

MORTALITY

The patients were divided into two groups by age, one below and one over 60 years at the onset of the disease. This choice of the 60-year limit is arbitrary. Each age group was then sub-divided according to sex, and a survival table was calculated (Nyholm & Helweg-Larsen) for each of these 4 groups (Table 2). Years of survival

Table 2.  
Survival table, computed for males and females with myelomatosis, divided into an over-60 and under-60 age group. For details see the text.

Duration of disease	Years of survival	Number of deaths	Death intensity	Survival percentage (myeloma)	Survival percentage (average population)	Group of patients
0				100	100.0	
1	25.7	2	.08	93±5.1	99.3	
2	20.3	5	.25	72	98.5	
3	17.2	6	.35	51±9.6	97.5	26 males under 60
4	10.9	4	.37	35	96.8	
5	7.5	1	.13	31	95.8	
6	6.0	1	.17	26	94.8	
7	5.0	1	.20	21±8.4	93.6	
1	19.8	10	.51	60±9.6	96.7	24 males 60 years and over
2	7.5	8	1.07	21	93.3	
3	3.1	4	1.29	6±4.3	89.5	
1	15.8	6	.38	68±10.6	99.2	
2	11.2	4	.36	48	98.4	
3	6.0	2	.33	34±11.4	97.5	19 females under 60
4	5.0	0	.00	34	96.6	
5	4.9	1	.20	28	95.6	
6	4.0	1	.25	22	94.5	
7	3.0	0	.00	22±10.1	93.4	
1	9.5	4	.42	65±13.8	97.3	11 females 60 years and over
2	5.2	4	.77	30	94.3	
3	3.0	0	.00	30±13.3	91.2	

(2nd column) denotes the number of years the total cases have survived during the interval concerned (1st column). By dividing the years of survival into the number of deaths (3rd column) during the interval concerned, we obtained the death intensity  $\mu_x$  (4th column). On the basis of  $\mu_x$  we can then compute the survival table (5th column) which shows the per cent of survivors after the years of disease given in the 1st column. The 6th column shows how the survival table would have been for persons whose age corresponded to the average age of the group at the onset of the disease and whose mortality corresponded to the mortality of the general Danish population 1941/45 (Statistique au Danemark 1949, p. 37). Thus, the difference between

the 4th and the 5th column reflects the excess mortality from multiple myeloma. Since no significant difference was demonstrable in the disease mortality for males and females, these groups were considered together — and the resulting curves plotted on Fig. 2.

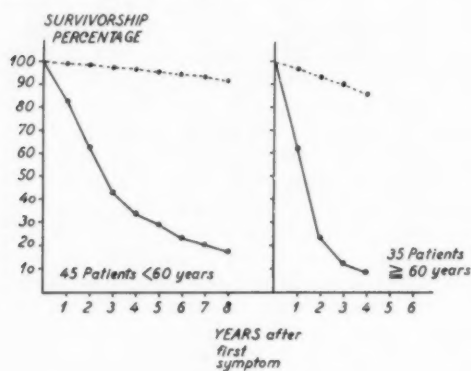


Fig. 2.

Survival curves (—) for 80 patients with myelomatosis, divided into two age groups. Abscissa: Duration from first definite sign until death. Ordinate: Per cent of patients still surviving. For comparison, survival curves (---) computed for persons of the same age and sex distribution, but with a mortality as in the general Danish population.

As might be expected, the excess mortality from multiple myeloma is very high, and it is higher for old than for young patients. While half the males and females who were under 60 years of age at the onset of multiple myeloma had succumbed within 2½ years, half the patients who were over 60 years of age at onset had died within 1½ years.

Even so, it is difficult or impossible to predict the individual prognosis with any degree of certainty. Although on the average the prognostic outlook seems to be poorer for elderly than for younger patients, the age at onset in the 13 patients who have had their disease for 5 years or over ranges from 25 to 61 years. Six of these 13 patients were 50 or over when the disease became manifest.

Thirteen patients survived for more than 5 years after the first manifestation. Since 62 patients have been followed up for a minimum of 5 years, this corresponds to a 5-year survival of 21 per cent.

On the average, the prognosis appears to be the same for patients with diffuse myelomatosis and for patients with multiple myeloma (i. e., the classic picture of multiple osteolytic foci).

Out of 16 patients with diffuse myelomatosis without demonstrable osteolytic changes, 13 died after an average illness of 1½ years, whereas 3 are still alive at the end of 1, 6, and 8 years.

Since electrophoretic studies were performed in only 14 cases, it is impossible to say whether the results of such study may be of assistance in evaluating the individual prognosis. Seven out of 10 patients with  $\gamma$  pattern on electrophoresis of the serum died after an average duration of 2½ years, while 3 are surviving at the end of 1, 1½, and 6 years, respectively. Four patients with  $\beta$  pattern have succumbed after an average duration of less than one year. Despite the small size of the group studied by electrophoresis, the results suggest that, as hinted by W u h r m a n n & W u n d e r l e y, the prognosis is on the whole better for patients with gamma myeloma than for patients with beta myeloma.

#### SUMMARY AND CONCLUSION

On the basis of a series of 80 patients with proven myelomatosis, it is endeavoured to assess the prognosis. The duration of the disease in 70 deceased patients is presented and survival curves are computed for all 80 patients and plotted in comparison with survival curves for a corresponding part of the general Danish population.

The 5-year survival is 21 per cent.

The mortality is the same for males and females, and it is higher for elderly than for younger patients. Half the patients in the younger age group had died at the end of 2½ years, while half the patients of the older group had died already the patients of the older group had already died within 1½ months.

The individual prognosis ranged from 2 months to 14 years and did not appear to depend on whether the myelomatosis was diffuse (without osteolytic foci) or characterized by multiple bone lesions. Perhaps the prognosis is poorer in cases where the myeloma cells produce beta globulins than for patients with so-called gamma myeloma.

Our thanks are due to the Danish Anti-Cancer League for economic support and to M. Nyholm, actuary, "Statistica", for statistical assistance.

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## THE ASSOCIATION OF THE FANCONI SYNDROME WITH MALIGNANT DISEASE

By P. J. DRAGSTED and NIELS HJORTH

Kidney diseases characterized by the failure of one or more renal tubular functions have attracted increased interest during recent years. The first type of disturbance to be described was glycosuria, but since then numerous reports have revealed other specific defects in the reabsorption of water, phosphate, bicarbonate, etc. Several of these anomalies may be found in combination, *viz.*, reduced reabsorption of glucose and phosphate, this being clinically manifested as osteomalacia with renal glycosuria. A highly complicated functional disturbance comprising glucose, amino acids and phosphate has been designated «Fanconi's syndrome.»

Reviews of such renal disorders have been given by Dent (2), Jackson & Linder (5) and Dragsted & Hjorth (3).

Details have thus far been published of 10 verified cases of Fanconi's syndrome (6). Some previous reports of osteomalacia with renal glycosuria cannot be definitely classified, as examinations of urinary excretion of amino acids were rarely undertaken prior to the introduction of paperchromatography by Dent (1946).

The incidence of malignant disease in the 10 reported cases of Fanconi's syndrome has been high. Stower's & Dent's patient (9) developed a primary cancer of the liver, and the authors note particularly the curious coincidence of a very rare renal disorder with a rare type of primary malignant disease. Another of the reported patients died from carcinoma of the pancreas (Meyerson & Pastor (6)), while a recently reported case was complicated with myelomatosis five years after the beginning of observation (Sirota & Haimerman (7)).

As the possibility of some unknown association between Fanconi's syndrome and malignant disease cannot be ruled out, it may be worth while to comment on the outcome of a case of Fanconi's syndrome already reported in detail on a previous occasion.

### CASE HISTORY

A business man, aged 49. In 1927 he had been treated with bismuth and salvarsan for syphilis, but otherwise he had been healthy until 1944 when proteinuria was incidentally disclosed. Examination in 1949 revealed the additional presence of glycosuria. He had no complaints until the spring of 1951 when a severe backache developed. In November, 1951, an X-ray examination of the chest showed multiple costal fractures of the Milkman type.

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(Chief physician: A. Hecht Johansen).

Subsequent examinations in January 1952 (cf. Table 1) revealed hyperchloremic acidosis, low serum calcium and serum phosphorus and increased alkaline phosphatases.

Urinanalysis revealed proteinuria, glucosuri and hypercalcuria. A paper chromatogram of the urine displayed several amino-acids (including serine, proline, histidine, tyrosine, lysine, valine and threonine).

Glucose tolerance test was normal with a rise up to 200 mg per cent, normal values within two hours. Basal metabolic rate was normal. Electrophoresis of serum proteins showed low values of gamma-globulin (0.18 per cent).

X-ray examinations showed multiple fractures of ribs and of the first and fourth right metatarsal bones.

*Course:* After two weeks of treatment with calcium phosphate, Shohl's mixture (citric acid + sodium citrate) and Vitamin D (50,000 units daily) the symptoms disappeared, and callus was observed around the fractures by X-ray examination. The treatment was continued for 13 months<sup>\*</sup>. In August, 1953, Vitamin D was discontinued as imminent intoxication was suspected. In December, 1953 he was readmitted on account of anorexia, loss of weight, impaired vision and lassitude.

Studies at this stage (cf. Table 1) showed an increased erythrocyte sedimentation rate, leucopenia with relative lymphocytosis, elevated acid phosphatases, and a diabetic glucose tolerance test with normal fasting blood sugar value.

A needle biopsy of sternal marrow now revealed a hyperplastic marrow infiltrated by plasma cells (84 per cent) and reticulum cells (11 per cent). Leucocyte-count of periferal blood was 3100 per mm<sup>3</sup>. Differential count was: neutrophils 53.5 per cent, lymphocytes 39 per cent, eosinophils 2 per cent, monocytes 39.5 per cent.

As the patient's condition gradually deteriorated treatment with ACTH (Acton prolongatum 40 units daily) was instituted. By this treatment an improvement of the general condition and of the vision was obtained, and the patient was discharged for continued treatment at home. A month later there was a tendency to epistaxis.

In March 1954 the patient was readmitted after having been febrile for two days with a temperature of 39° C. (102° F.).

On account of the intercurrent infection, treatment with ACTH had been discontinued. On admission a diagnosis of bronchopneumonia was made and a penicillin treatment was instituted.

Treatment with ACTH or cortisone was not resumed, and in spite of blood transfusions and potassium infusion the patient died twenty-four hours later.

At autopsy the lungs were oedematous and congested, the spleen and bone marrow were hyperplastic. The liver showed patches of acute yellow atrophy.

<sup>\*</sup> For a detailed description of the course see (4).

Table 1.

	Jan. 52	June 53	Nov. 53	Jan. 54	March 54
<b>Blood</b>					
Haemoglobin %	109	96	73	50	50
Serum iron (gm <sup>0</sup> /o)		0,183	0,226	0,271	
ESR (mm/hour)	8	13	56	58	
Blood urea (mg <sup>0</sup> /o)	27	20	27	45	50
Urea clearance	59—45	52—59	55—61		
Serum phosphorus (mg <sup>0</sup> /o)	2.4	2.3	2.9	5.2	
Serum calcium (mg <sup>0</sup> /o)	8.8	9.7	9.7	9.1	
Alkaline phosphatases (Buch units)	12.5	8.5	8.2	7.6	
Acid phosphatases (Gutman units)	3.0	5.0		2.2	
Fasting glucose (mg <sup>0</sup> /o)	80	95	100	95	
Albumin/Globulin ratio (o/o)	4.8/1.1	4.9/1.6	4.7/1.6		
Total protein (o/o)				5.8	5.5
<b>Electrophoresis:</b>					
Albumin + Alpha (o/o)	4.00		3.87	2.90	2.98
Alpha <sub>2</sub>	0.51		0.68	0.97	0.64
Beta	0.37		0.75	0.70	0.68
Gamma	0.46		0.20	0.12	0.00
Serum sodium (mEq)	146	142	146	144	146
Serum potassium (mEq)	4.7	4.6	4.1	3.9	2.3
Chloride (mEq)	106	111	99	113	110
Bicarbonate (mEq)	16	21	19	19	18
Serum amino acids (mg <sup>0</sup> /o)		9.0		11.8	
<b>Urine</b>					
Specific gravity (max.)	1016		1015	1017	1010
Proteinuria (o/o)	0.5	0.6		0.6	
Glucosuria (o/o)	1.5	1.2	1	2.5	0.33
Phenolsulphthalein excretion (in percentage)	17+16	6+8	6+9		

The parathyroid glands were not examined. The histologic examination is incomplete due to putrefaction. In the preserved cells of the liver a moderate accumulation of lipoids was noted. The glomeruli of the kidneys varied in appearance, some were hyaline, but the majority were highly cellular and mostly empty of blood. Contorted tubuli showed degenerative changes, and in the lumina of nearly all straight ducts deeply stained homogenous and granular casts were found. There was an increase in the interstitial connective tissue. Examination of the suprarenal glands revealed a slightly hyperplastic cortex with cells rich in lipoids but without definite pathologic changes. Bone-sections from the spine revealed extreme hyperplasia of the marrow with 98 per cent plasma cells, while bone structure was normal.

**Epicrisis:** A 49 year old business man. In 1927 adequately treated for lues with bismuth and salvarsan. Since 1944 proteinuria and from 1949 furthermore renal glycosuria. In 1951 a backache lead to the detection of multiple costal fractures. Examination during stay in hospital January—April, 1952, showed hyperchloremic acidosis, low serum phosphorus and serum calcium increased alkaline phosphatases, proteinuria, glycosuria and aminoaciduria.

On treatment with calcium phosphate, Shohl mixture and Vitamin D the backache disappeared and the fractures healed.

In December 1953 repeated examination because of lassitude and loss of weight. Sternal puncture now showed myelomatosis. The patient died three months later from intercurrent infection. At autopsy changes typical of myeloma were found.

#### DISCUSSION

The question seems to suggest itself whether the pathological fractures might have been due to myelomas. This assumption is however hardly likely, as the examination revealed a combination of renal functional disturbances which must inevitably lead to osteomalacia. An adequate treatment of the renal osteomalacia led to a rapid healing of the fractures.

Like the case reported by Sirota & Hamarman (7), our patient presented the typical features of Fanconi's syndrome, and both patients later developed myelomatosis. These two patients showed a coincidence of two diseases of such rareness that invariably the question is asked whether any causal connection exists, i. e., whether the tubular functional disturbance might be a rare manifestation of myeloma kidneys or whether the Fanconi syndrome was a predisposing factor to the malignant disease.

In myelomatosis abnormal proteins are accumulated in the cells of the renal tubules leading to an impairment of function involving *inter alia* a reduced excretion of phenolsulfthalein. It should be stressed, however, that in the most extensive reports of myelomatosis (8), no cases of renal glycosuria are cited. Though normal values of serum calcium and serum phosphorus are the rule, exceptional cases show a low serum phosphorus. Possibly such low levels may be the result of deficient reabsorption of phosphate, which would lead to osteomalacia. Patients suffering from myelomatosis and pathological frac-

tures are, however, rarely examined with this possibility in mind.

If indeed Fanconi's syndrome should be a clinical manifestation of the renal tubular insufficiency in myelomatosis, it must be extremely rare.

Sirota & Hamarman's patient suffered from proteinuria for three years, our patient for seven years, before the symptoms of osteomalacia developed. But at this time none of the patients presented any symptoms of myelomatosis. In spite of repeated bone marrow studies, the possibility cannot be excluded that the patients have had a latent myelomatosis for many years which was only reflected in the proteinuria. The observed low gamma globulin values, which are characteristic of myelomatosis (1), support this view.

Myelomatosis is not the only malignant disease that has been described in association with Fanconi's syndrome. One should therefore consider whether this type of renal tubular insufficiency might predispose a subject to malignant diseases. In animal experiments, deficiency of certain amino acids has accelerated the growth of tumors of the liver. Similarly, a continued loss of essential amino acids might interfere with the protein synthe-

sis of some cell types, so that the differentiation of the cell is inhibited and malignant cells finally are formed.

A disturbance of the protein synthesis of certain tissues might well account for the remarkable incidence of congenital malformations in children with Fanconi's syndrome.

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## LYSIS OF ARTIFICIAL THROMBI BY PLASMIN PRODUCED BY ACTIVATION WITH THE URINE ACTIVATOR

By OLE STORM

The risk of thromboembolic diseases has been considerably decreased since the introduction of an effective prophylaxis with anticoagulants. However, in the resolution of thrombi already present, the effect of a treatment with anticoagulants depends essentially on the natural thrombolytic processes of the organism (Astrup, 1954). Furthermore, blood coagulation and the deposition of fibrin in the organism during treatment with anticoagulants are not, and because of the inherent danger of haemorrhage should not be, completely annihilated. Therefore the risk of embolic complications still exists until ways have been found for instituting an active therapy aimed at a safe and complete resolution of any intravascular clot.

The fibrinolytic system in the organism is the system chiefly responsible for the thrombolytic activity. This system involves a precursor (plasminogen) of a proteolytic enzyme in blood (plasmin). The precursor can be transformed into the active enzyme by different activating agents, among

which are compounds present in certain tissues, in urine, and in blood. The activating agents in blood is formed from a precursor (a proactivator), and this transformation can be effected by a metabolic product from certain strains of haemolytic streptococci (streptokinase) (see Astrup, 1956a for references).

Lysis for experimentally produced thrombi in rabbits has been attempted by the intravenous introduction of streptokinase alone (Johnson & Tillet, 1952) or in mixtures with preparations of human plasminogen (Cliffon, Cannamela & Grossi, 1953, 1954, Grossi, Cliffon & Cannamela, 1954). Streptokinase contains material of bacterial origin and serious side-effects have been observed after its introduction into the blood stream of rabbits (Johnson & Tillet 1952) or in human beings (Tillet, Johnson & McCarty, 1955). Human urine contains an activator of plasminogen which can be partially purified and prepared as a dry product (Astrup & Sterndorff, 1952, 1955).

The purpose of this paper is to demonstrate that lysis of experimentally produced thrombi in rabbits can be obtained by means of plasmin prepared by

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activation of human plasminogen solutions with an activator from human urine. In this manner, thrombolysis is obtained by a protease solution containing only components of human origin.

#### MATERIALS AND METHOD

Human globulin was precipitated isoelectrically from human serum and redissolved in phosphate buffer (pH 7.65) to  $\frac{1}{5}$  of the original volume (Müllertz, 1955). This preparation contains plasminogen and the precursor of the plasminogen activator. The plasminogen activator from urine was prepared from fresh human urine as described before (Astrup & Sternedorff, 1952). The dry preparations made in this manner varied in potency but contained about 60 per cent of the original activity in the urine as estimated by the fibrin plate method (Astrup & Müllertz, 1952). Samples of more highly purified preparations of the urine activator were also used. These — as well as the bovine thrombin used — were kindly supplied by the Løvens kemiske Fabrik, Copenhagen. The streptokinase ("Varidase") used in some experiments was kindly supplied by the Lederle Laboratories. The plasmin solutions were prepared by incubating the human globulin solution (as prepared above) for 15 mins. at 37° with the urine activator. The optimum amounts needed were estimated in separate experiments for each lot. The plasmin activity was estimated on casein (Müllertz, 1955).

The thrombi were produced in rabbits in the marginal vein of the ear by injection of approximately 0.1 ml of a 5 per cent sodium morrhuate solution (kindly supplied by Dr. Helen Payling-Wright, London). The solid clot formed in this way was 1–2 cm in length and appeared firmly attached to the walls of the vessels. Clots formed with thrombin are more loose, do not attach well to the walls and are not as easily reproduced as the morrhuate clots. In a few experiments a mixture of thrombin and sodium morrhuate was used, but the clots were loose in structure, and in one case (an untreated control animal) it disappeared spontaneously.

The formation of the thrombi was studied by means of photographic recording by X-ray after introduction of a contrast solution ("Diodon"). Observations were also made by transillumination and injection of saline. In most experiments the contrast solution or the saline was introduced through a polyethylene catheter placed in the marginal or central vein of the thrombosed ear at some distance from the thrombus. In some experiments the solutions were introduced by venous puncture at the tip of the ear.

The plasmin solutions were injected intermittently intravenously in the other ear. The administration of plasmin was begun  $\frac{1}{2}$ –24 hours after the formation of the thrombus. Five to ten ml plasmin solution were injected in the beginning and the injections were repeated at half hour intervals, see Table 1.

The effect of the treatment was followed by transillumination or by venography as described above. The animals were anesthetized with Nembutal by intravenous administration. Photographic X-ray re-

cordings were made 1–3 hours after the injection of plasmin and also at the moment when the thrombus, by visual inspection by transillumination, appeared lysed.

A series of animals prepared as described, but in which no injections or only injections of saline were given after the thrombus formation, served as control. The natural thrombolysis was followed in these animals by X-ray examination as described above.

In a few animals the plasmin activity of the blood was followed. Blood samples were withdrawn at five minute intervals after the plasmin injection. After centrifugation and isoelectric precipitation of the plasma, the precipitate was dissolved in phosphate buffer (pH 7.65; half original volume). The activity was estimated on heated fibrin plates in order to exclude any effect of plasminogen activators in the blood (Lassen, 1952).

Table 1.  
Effect of plasmin on artificial thrombi in the rabbit.

No.	weight in kg	clot length (cm.)	hours before plasmin injection	plas- min ml	lysis time (hours)
1	1½	1	½	5	+1
2	2½	1	½	10	+1½
3	3	1	1	15	+2
4	3.3	1	1	10	+1
5	4.8	1	1	40	+3
6	2	1½	3	15	+2
7	3.2	1	3	10	+1
8	2	1	3½	15	+2½
9	3	2½	4	30	
10	2.2	1½	4	12	+3
11	3.3	1	4	10	+3
12	2.5	1	5	5	+1
13	2	2	24	20	+3
14	3	1	24	10	+2

Table 2.  
Control group of rabbits with artificial thrombi.

No.	weight in kg	clot length (cm)	lysis	time of obser- vation (hours)
1	3	1	÷	4
2	2	1	÷	24
3	2	1½	÷	6
4	2.2	1	?	4
5	2	1	÷	3
6	2.5	½	÷	5
7	5	1	÷	4
8	3.5	1	÷	5
9	2.6	1	÷	4
10	2.9	½	÷	4
11	2.5	1	?	1½
12	3.5	1	÷	1

#### RESULTS

In preliminary experiments (4 animals) with plasminogen preparations activated by addition of streptokinase the thrombolytic effect observed by Clifton et al. (1. c.) could be confirmed.





Fig. 1.

Phlebogram of ear vein of plasmin treated rabbit No. 10. The contrast medium had been injected in the distal part of the marginal vein. Obstruction of the vessel by the thrombus is clearly shown.



Fig. 3.

Phlebogram of control rabbit No. 3 one hour after formation of the thrombus. No passage.



Fig. 2.

Phlebogram of ear vein of plasmin treated rabbit No. 10 3 hours after beginning of the plasmin injection. Partial filling of the previously thrombosed vein is apparent.



Fig. 4.

Phlebogram of control rabbit No. 3 six hours after the formation of the thrombus. In spite of injection of contrast medium close to the clot there is no passage.

Plasmin solutions prepared with the urine activator were given to 14 animals (Table 1). In 13 of the animals recanalization was demonstrated by the free flow of the contrast medium through the previously obstructed vein. In one of the animals (Table 1; rabbit No. 9) no lysis could be demonstrated in spite of repeated doses of plasmin. Three died from pulmonary embolism (Table 1, Nos. 7, 8 and 11) and in two the death was caused by the anaesthesia (Table 1, Nos. 2 and 9). The pulmonary embolism in the first three cases occurred immediately after the venography. The cause could be either an embolus from the thrombosed vein or it could be intravascular coagulation produced by the injection of the contrast medium 50-70 per cent concentrated "Diodon". In two cases oozing of blood from the needle puncture in the ear occurred but with no further side-effects.

The control group consisted of 12 animals (Table 2). Spontaneous recanalization occurred in one case (Table 2, No. 2). In two cases the clot formation was less than normal and the lysis could not be exactly observed (Table 2, Nos. 4 and 11). None of the animals in the control group died.

In some of the experimental animals the plasmin concentration in the blood was followed after the injection, as described above. Maximum activity was found immediately after the injection and the fibrinolytic activity decreased gradually during the next 30 minutes (Fig. 1). When the plasmin injection was repeated, an increased activity was again observed.

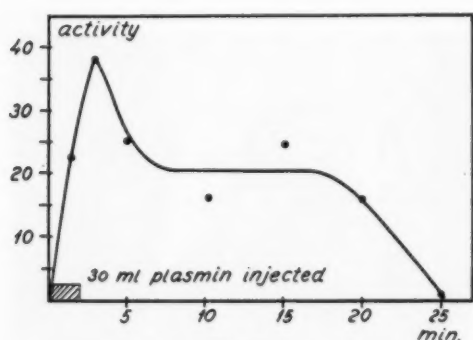


Fig. 5.  
Disappearance of injected plasmin from the blood stream.

Rabbit No. 5: Plasmin activity in blood measured on heated fibrin plate, after isoelectric precipitation. Ordinate: activity; the area of the lysed zones. Abscissa: time in minutes.

#### DISCUSSION

The results here described confirm the observations made by previous authors that potent solutions of human plasmin, when injected intravenously, are able to lyse experimentally produced thrombi in rabbits. The experiments show that

preparations of plasmin made from human plasminogen by means of the plasminogen activator in human urine have sufficient lytic effects. These preparations contain proteins of only human origin and this would probably constitute an advantage in human therapy. The plasmin activity disappears rapidly from the blood stream, and in cases where an activity is needed for a longer period the administration has to be repeated every half hour.

In the resolution of artificially produced thrombi, trypsin has been tried with diverging results by Innerfield, 1952; and Roach & Laufman, 1954. Plasmin is probably the ideal enzyme for this purpose because it is the physiological enzyme of the organism and is especially adapted to the purpose of the resolution of fibrin. It is absorbed on the fibrin and therefore escapes to a certain extent the effects of the inhibitory compounds present in the blood. Trypsin is much more sensitive to the inhibitory agents than plasmin is. As mentioned before, (Astrup, 1954) the urine activator might also be useful in the resolution of thrombi. However, this possibility depends on the amount of plasminogen present in the organism because no additional protease precursor is introduced. Also the inhibitory agents acting against the activation of plasminogen will have full effect in this case. Therefore it is probably not surprising that in our own preliminary experiments the introduction of urine activator alone in the rabbits had no significant effect on the thrombi (Storrm, 1956). Apparently the rabbit is not a very suitable animal for investigations of this kind because the amounts of plasminogen in rabbit blood are low and the inhibitory effect is very pronounced (Astrup, 1956 b). This conforms with the large amounts of streptokinase needed in the experiments of Johnson & Tillett (1952), which can be explained by the low content of activator precursor in rabbit blood. It can also be mentioned that the rabbit is very resistant to injections of adrenalin, which produce high fibrinolytic activity in human beings (Williams, 1951).

In one of the animals (No. 9) the thrombus did not lyse. From the table it is seen that the thrombus produced in this animal was the largest of all. This case exemplifies probably another problem in the use of proteases in the resolution of thrombi in vivo. In order to exert its effect the enzyme must come into close contact with the fibrin clot. If the circulation is prevented so that the enzyme does not reach the clot in sufficient amounts, the clot will eventually persist in the organism. This applies especially to those cases where the blood flow in the obstructed vein is completely prevented, so that the enzyme acts only on the end of the clot. The difficulties in an effective lysis in a short time are apparent in such cases. The cases of fatal embolism encountered in the experimental group reveal another difficulty in the method. These cases most probably occurred

by partial lysis of the solid clots followed by loosening from the adherence to the vessel wall. The embolus thus formed is carried with the re-established blood stream to the lungs. Also the high concentrations of the X-ray contrast medium applied might cause lung emboli, but this is apparently not the case in the material here described, since the control material, which received similar injections, did not produce a single fatal case. As far as can be seen from these experiments, the risk of embolus formation is an inherent danger of the procedure. This is a difficult problem especially in venous thrombosis. In the case of arterial thrombosis the problem might be different, though also here there is a risk of embolism caused by small fibrin clots breaking off from the main thrombus and depositing themselves at different parts of the arterial system before they have been completely lysed. The question will be discussed in detail elsewhere. It must be given careful consideration before the method is introduced as a treatment in human beings. The age of the thrombus might be expected to be of significance, but in our cases no significant differences were observed between fresh thrombi and 24 hour old thrombi. However, more experimental material is needed to settle this question.

#### SUMMARY

Preparations of plasmin have been made from human plasminogen and human urine activator. The active solutions produce lysis of artificially induced thrombi in rabbits. The experiments demonstrate a risk of embolism by the application of lytic solutions. Some problems of significance

in the evaluation of the method as a safe therapeutic treatment are pointed out.

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## PERCUTANEOUS MEASUREMENT OF PELVIC BREADTH IN NORMAL AND OBESE CHILDREN

By FLEMMING QUADE

In 1925 Wingate Todd dissected a number of human corpses in order to estimate the reliability of measurements based upon subcutaneous bony points. He found that even in a superficial bony prominence like the anterior superior iliac spine, the intervening skin and other soft tissues cause an error amounting to 5 mm in the measurement of the bi-spinous diameter. A needle for measuring the thickness of superficial soft tissues has been described by Martin (1928), but the instrument is intended to be used post mortem. Skinfold calipers, used on living subjects, yield reliable results in the hands of a trained examiner (Edwards 1950 and 1951, Skerlj et al. 1953), but are only suitable for regions where the skin and subcutaneous fat are loose enough to allow the instrument to be applied freely. Accordingly, calipers are of little value in measuring the thickness of soft tissues covering the iliac crests, where skin and subcutis are firmly bound to the underlying bone, both in normal and obese individuals. The bi-cristal diameter is widely used in the estimation of pelvic breadth because the iliac crests are easy to localize, but even in normal or thin individuals, and even with firm pressure, there will be an inevitable interposition of soft tissues between the branches of the caliper, and it is safe to assume that this error is considerably increased in obese subjects.

The present investigation was carried out in order 1) to evaluate the size of this error, and 2) to see whether any possible differences between the pelvic breadths of normal and obese children — as measured with the ordinary caliper — could be due solely to the interposition of a more plentiful subcutis in the obese individuals.

The material consisted of the aggregate number of children frequenting one Copenhagen City Council school, i. e., 1082 subjects (533 boys, 549 girls) between 6 and 16 years of age. Among these, 84 children (44 boys, 40 girls) were clinically obese, but only moderately so. The material was therefore supplemented with a group of 104 obese children, of whom 51 (18 boys, 33 girls) were selected as the fattest from eight Copenhagen City Council schools; the remaining 53 (25 boys, 28 girls) were also schoolchildren, but taken from an out-patient Pediatric Service where they were under treatment for obesity. Although broad hips and seemingly feminine proportions were common in these boys, and many of them had been referred to the clinic with the diagnosis of adiposo-genital dystrophy, there was no other evidence of endocrine disorders, and the total

number of obese children — 188 boys and girls — were therefore treated as one group.

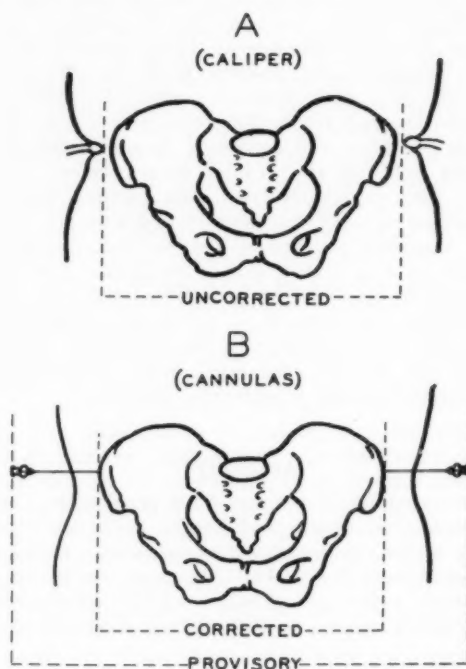


Fig. 1.  
Illustration of technique.

15 obese children — admittedly not equally distributed in regard to sex (10 boys, 5 girls) — but in other relevant respects (age, height, degree of overweight) representative of the total group, were selected for percutaneous measurement of pelvic breadth; so was a small control group of 6 non-obese children (4 boys, 2 girls). First, the bi-cristal diameter was determined in the usual way, the branches of the caliper being pressed very firmly against the bone (Fig. 1 A), and the measuring-points were marked with iodine. Through these points were then stuck thin, but stiff cannulas horizontally through the integuments to the lateral borders of the iliac crests, and with the caliper a provisory measure was taken between the ends of the two needles, while an assistant held the cannulas in their right position. The corrected bone measure was found by subtracting the total length of the cannulas from the provisory measure (Fig. 1 B), and the difference between the corrected measure and



the uncorrected bi-cristal diameter was taken as an expression of the error occasioned by the soft tissues interposition. It goes without saying that the examination is somewhat unpleasant for the children and takes much more time than the ordinary method. Table 1 gives the data of the 21 children:

Table 1.  
*Individual and average soft tissues corrections for 15 obese and 6 non-obese children whose bi-cristal diameters were measured with cannulas and caliper.*

Sex	Age	Height cm	Weight kg	Weight- deviation kg	Bi cristal m.m. corr.	uncorr.	Correc- tion mm	Average corr. mm
<b>Obese</b>								
Boy	8	128	32.7	7.0	178	207	29	
"	8	139	40.0	8.1	202	238	36	
"	10	140	39.0	6.4	224	246	22	
"	11	141	47.7	14.5	195	225	30	
"	14	146	42.1	5.6	213	240	27	
"	10	147	45.5	8.3	216	240	24	
"	12	150	55.5	16.3	211	245	34	
"	13	153	54.5	13.0	220	252	32	
"	13	160	56.2	8.9	233	257	24	
"	12	162	67.0	18.1	224	270	46	30
Girl	10	134	48.1	18.9	189	230	41	
"	10	141	44.1	10.6	182	237	55	
"	10	142	48.0	13.9	185	238	53	
"	13	154	59.9	16.0	256	280	24	
"	12	160	68.6	18.8	214	283	69	49
<b>Non-obese</b>								
Boy	10	139	29.2	-2.7	199	216	17	
"	11	146	35.2	-1.3	215	231	16	
"	12	147	40.0	2.8	222	241	19	
"	14	161	47.0	-1.1	244	257	13	16
Girl	9	141	27.7	-5.8	201	214	13	
"	15	161	57.4	6.6	255	283	28	(21)

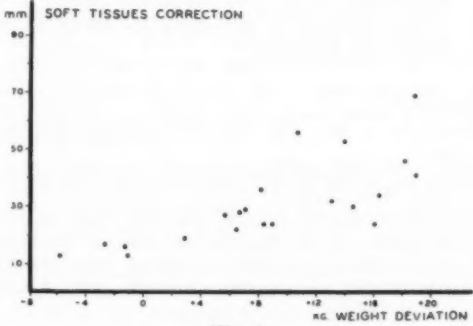


Fig. 2.  
*The relationship between soft tissues' correction (in mm.) and absolute weight deviation (in kg.) in 15 obese and 6 non-obese children whose bi-cristal diameters were measured with cannulas and caliper.*

Both individual and average corrections are greater in the obese group than in the control children, and Fig. 2 shows that no doubt there is a tendency for increasing overweight to be correlated with increasing thickness of skin and

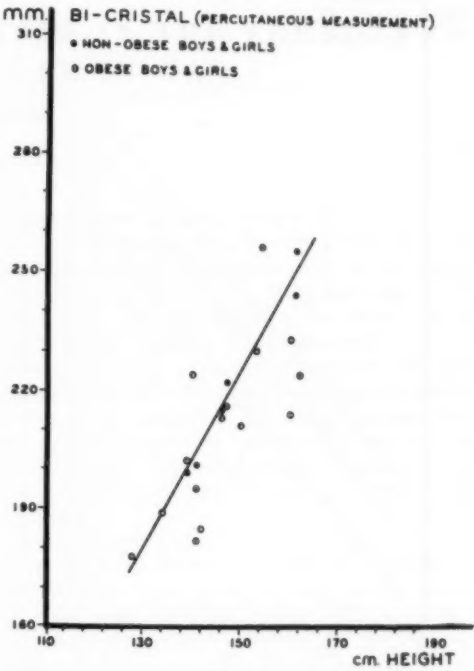


Fig. 3.  
*The relationship between stature and corrected bi-cristal diameter for 21 children, 15 obese (circlets) and 6 non-obese (dots).*

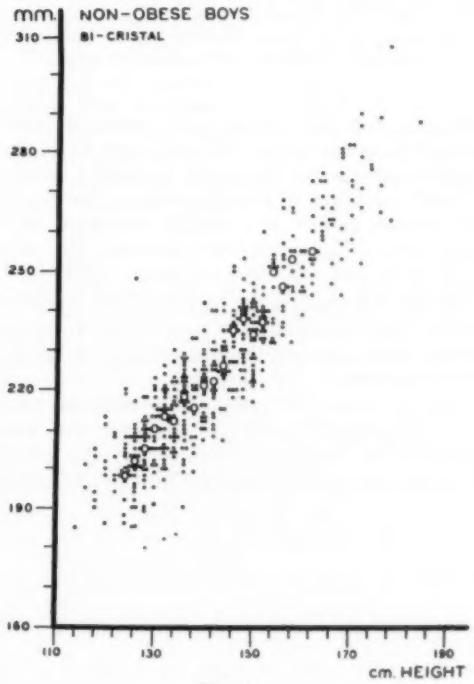


Fig. 4.  
*The relation between stature and uncorrected bi-cristal diameter for the total material of 489 non-obese boys. (Circlets: mean values for the height groups).*

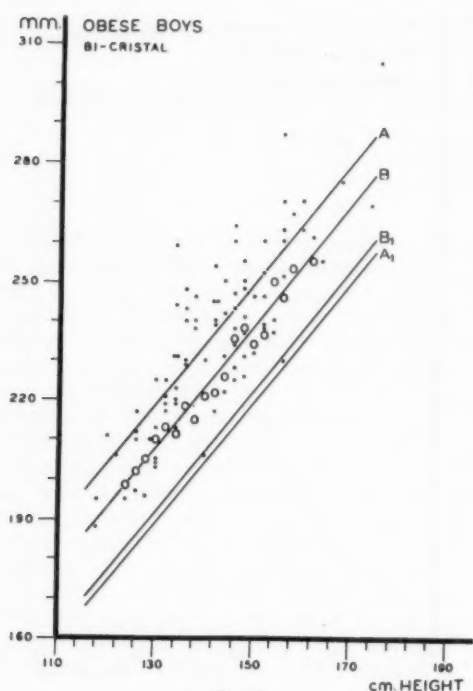


Fig. 5.

The relation between stature and uncorrected bi-crystal diameter for the total material of 87 obese boys. (A: mean values for the obese material; circlets and B: mean values for the non-obese material. A<sub>1</sub> is lower than A by 30 mm. — the average correction for obese boys; B<sub>1</sub> is lower than B by 16 mm. — the average correction for non-obese boys).

subcutis, but the points are scattered widely around a straight line. This was only to be anticipated, seeing that the group comprises children of both sexes and of varying heights, and because we cannot expect the weight deviation of an individual to indicate with accuracy the thickness of fat and subcutis in a single place.

In Fig. 3 the values for corrected pelvic breadth of the obese children are seen to be distributed fairly evenly around the normal line of the non-obese subjects.

Fig. 4 shows the relationship between height and uncorrected pelvic breadth for the whole material of non-obese schoolboys; the circlets indicate the mean values for the height groups.

These mean values are indicated also in Fig. 5, which shows the pelvic breadth/height relationship for the total group of 87 obese boys. It will be seen that the measure, as determined with the caliper alone, shows an unmistakable tendency towards high values for the obese boys. In order to see whether this finding bespeaks any real peculiarity in the skeletal dimensions of obese boys, the figure was provided with four parallel lines: A and B give the mean values for the obese and the non-obese materials respectively; A<sub>1</sub> and B<sub>1</sub> symbolize the cannula measures after applying the average corrections — 30 and 16 mm — obtained for the two groups of boys in Table 1. A<sub>1</sub> and B<sub>1</sub> are so close to one another that we are justified in regarding the difference between the caliper measures as being due solely to the interposition of a greater amount of subcutaneous fat in the obese boys. The materials of girls need not be illustrated, because they showed the same characteristics as the boys.

The results justify the following conclusions:

- 1) The bi-crystal diameter can be determined more correctly by means of cannulas than with calipers alone, but the percutaneous technique is too slow and unpleasant to be used as a routine method.
- 2) The layer of subcutaneous fat, also in the regions of the iliac crests, is much thicker in obese than in non-obese children.
- 3) The bi-crystal diameter, as measured with the ordinary caliper method, is decidedly smaller in non-obese children than in a material of obese children in whom a diagnosis of endocrine disorder had been considered.
- 4) The difference observed in 2) seems to be sufficient explanation of the finding mentioned in 3), and we must assume that pelvic breadth is the same in obese as in non-obese children.

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## ANTI GIZZARD ULCER FACTORS IN THE TREATMENT OF GASTRIC ULCER IN MAN

### A REVIEW

By ERLING LUND

Nutritional development and prevention of ulcer in the muscular stomach (gizzard) of chicks has been described in several publications, such as those by Dam (1934, 1946), Dam & Schønheyder (1934), Dam & Segal (1945), Dam, Noer & Søndergaard (1950), Cheney (1938, 1940, 1942).

Dam and associates produced gizzard ulcers with bleeding or perforation, often severe, by feeding chicks an artificial diet containing cod liver oil. Addition of hog liver, calf's brain or certain extracts thereof to the diet caused marked protection. The protective effect could be obtained by the combination of two fractions (anti-gizzard ulcer factors), *viz.*, lipid extract from calf's brain and the residue from the extraction. The residue could be replaced by an aqueous extract of calf's brain or by Vitamin B<sub>12</sub>.

Based on these prophylactic experiments with chicks, attempts have been made to treat human gastric and duodenal ulcer with preparations largely consisting of "anti gizzard ulcer factors". One such preparation contains these factors in the form of "nonsteridic" extracts of cattle organs mixed with dehydrated cream and milk, vitamins, iron and flavoring material, etc. In the U. S. A. and Canada a preparation of this kind is for sale in tablet form at a high price under the name of "Exul" or "Nupra". Sensational praise of this preparation has been spread in newspapers, magazines and on the radio, saying that it has a miraculous effect on human ulcer which may be cured in a few days merely by taking these tablets. Some of the statements have even hinted that Professor Dam has communicated such results. Dam (1954 a, b, c) has clearly repudiated this insinuation.

During the last two years thorough clinical trials have been carried out in Denmark in order to evaluate the utility of "anti gizzard ulcer factors" in the treatment of gastric and duodenal ulcer in man. Brøchner-Mortensen, Krarup, Meulengracht & Videbæk (1955 a, b) examined two randomly chosen, approximately equal groups of patients (152 in all). In one of the groups the patients received a purée diet plus ether extract of calf's brain and Vitamin B<sub>12</sub> with added intrinsic factor, while the other group received the same purée diet plus a placebo preparation not containing the anti-

gizzard ulcer factors. Lund & Krohn (1955, 1956) have made trials in which one group of 18 patients was treated solely with a dietetic preparation containing a decholesterolized ether extract of calf's brain and the ether extracted calf's brain admixed with dehydrated milk and cream, vitamins, etc. (a composition corresponding to the preparation "Exul"), whereas the other group of 18 patients received a preparation of the same composition except that the two "anti ulcer factors" were replaced by milk powder. The preparations had an energy content of 6000 cal./kg.

Both sets of trials showed that the same results were obtained whether or not the chicken anti ulcer factors were given, in spite of the fact that in each case the prophylactic efficiency in the chicken test had been ascertained. At the end of treatment freedom from subjective symptoms was obtained in up to 94 per cent of the patients, and radiological signs of ulcer (niche, deformation of the duodenal cap) disappeared in up to 50 per cent of the cases. The results were not better than those resulting from the commonly used dietetic ulcer treatment.

Thus no specific curative effect of "anti gizzard ulcer factors" against human gastric or duodenal ulcers could be found in any of the trials.

It is not surprising that a dietetic preparation containing dehydrated cream and milk can be used in treatment of human ulcers, since milk is an essential part of many ulcer diets.

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 Chief: Tage Bjering.

TOBACCO CONSUMPTION IN DENMARK. II.

THE DANISH NATIONAL MORBIDITY SURVEY OF 1950.  
COMMUNICATION NO. 12

By HENRY HAMTOFT and MARIE LINDHARDT

In an article on the consumption of tobacco in Denmark\*), founded upon information secured in the course of the Danish National Morbidity Survey of 1950, we gave an account of the number of smokers by sex and age in relation to the form and quantity of the tobacco. The analysis applied to the entire population of the country.

In the present article we propose to show the differences in the *smoking habits of the populations within the main geographical sections of the country*, according to the information obtained in the period from August, 1952, to April, 1953. In the first four months of 1954 inquiries were again made about smoking habits, sup-

plemented with questions as to to what extent smoke was inhaled and at what age the smokers began to use tobacco regularly.

Table 1 provides a survey of male smokers in the capital, the provincial towns and the rural areas, a distinction being made between the form of tobacco smoked. There is most smoking in the capital, where 82 per cent of all adult males admitted to being smokers, compared with 79 per cent of the males in the provincial towns and 74 in the rural areas. As might have been expected about the population of a large city, cigarette smoking predominates there, whereas the rural population smoke the fewest cigarettes and the provincial towns lie midway between the two extremes. Conversely, pipe smokers are in the majority in the rural areas and are fewest in the capital, the provincial towns again occupying an intermediate position; see also Fig. I. In the first article we distinguished between cigar

\*) See Danish Medical Bulletin, vol 2, no. 7, December 1955.

From the Committee on the Morbidity Survey.  
Chairman: *Johs. Frandsen*.

Table 1.  
*Male Smokers by Form of Tobacco for each Province and all Denmark.*  
August 1952 — April 1953.

	Size of sample			In per cent of all interviewed males					
	total	of which smokers	all smokers	cigarette smokers	pipe smokers	cigar smokers	cigarillo smokers	all non-cigarette smokers	non smokers
Capital .....	3,277	2,671	81.5	36.4	28.9	6.9	9.3	45.1	18.5
Provincial towns .....	3,473	2,748	79.1	25.3	37.4	6.9	9.5	53.8	20.9
Rural districts .....	4,742	3,517	74.2	13.0	45.3	7.5	8.4	61.2	25.8
Whole country .....	11,492	8,936	77.8	23.4	38.2	7.1	9.0	54.3	22.2

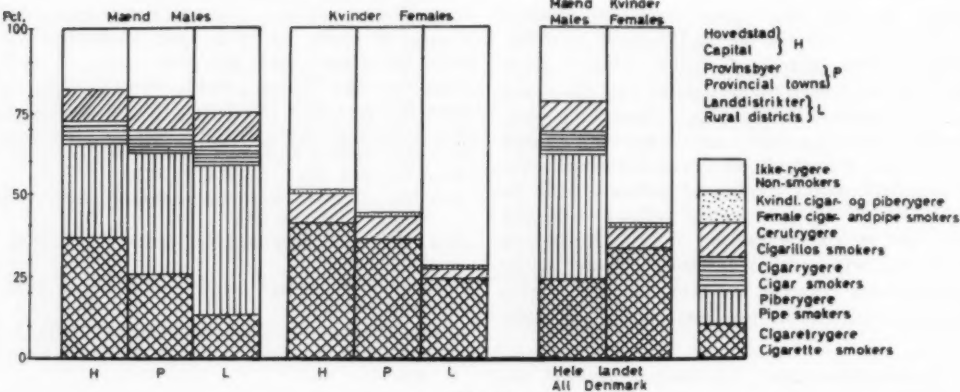


Fig. I.  
*Smoking Habits in Denmark by Provinces in 1952-53 according to Sex and Form of Tobacco.*



Table 2.  
Age Distribution of Male Smokers by Form of Tobacco for each Province and all Denmark.  
August 1952 — April 1953.

In per cent of all interviewed males												
Age	Capital		Provincial towns			Rural districts			Whole country			
	Cigarettes	Pipe	Cigars and cigarillos	Cigarettes	Pipe	Cigars and cigarillos	Cigarettes	Pipe	Cigars and cigarillos	Cigarettes	Pipe	Cigars and cigarillos
15—19 years ..	43.6	20.9	0.4	29.6	30.7	—	18.8	40.2	0.2	28.3	32.5	0.2
20—29 " ..	47.0	34.0	2.3	36.6	45.5	2.9	23.2	54.4	2.1	35.1	45.0	2.4
30—39 " ..	47.1	27.3	12.1	33.6	42.5	10.5	17.3	54.1	10.8	31.6	43.1	11.1
40—49 " ..	39.3	26.9	19.2	30.0	34.2	19.6	15.5	45.8	19.2	26.6	37.0	19.4
50—59 " ..	27.8	23.8	30.9	19.0	34.2	27.0	5.7	40.5	29.5	15.6	34.2	29.1
60—69 " ..	12.5	35.8	30.3	5.2	32.0	35.1	1.9	34.8	26.3	5.6	34.2	30.0
70 years a. o. .	2.8	34.1	28.1	2.3	35.5	20.8	1.4	35.6	20.0	2.0	35.0	22.2
Total .....	36.4	28.9	16.2	25.3	37.4	16.4	13.0	45.3	15.9	23.4	38.2	16.1

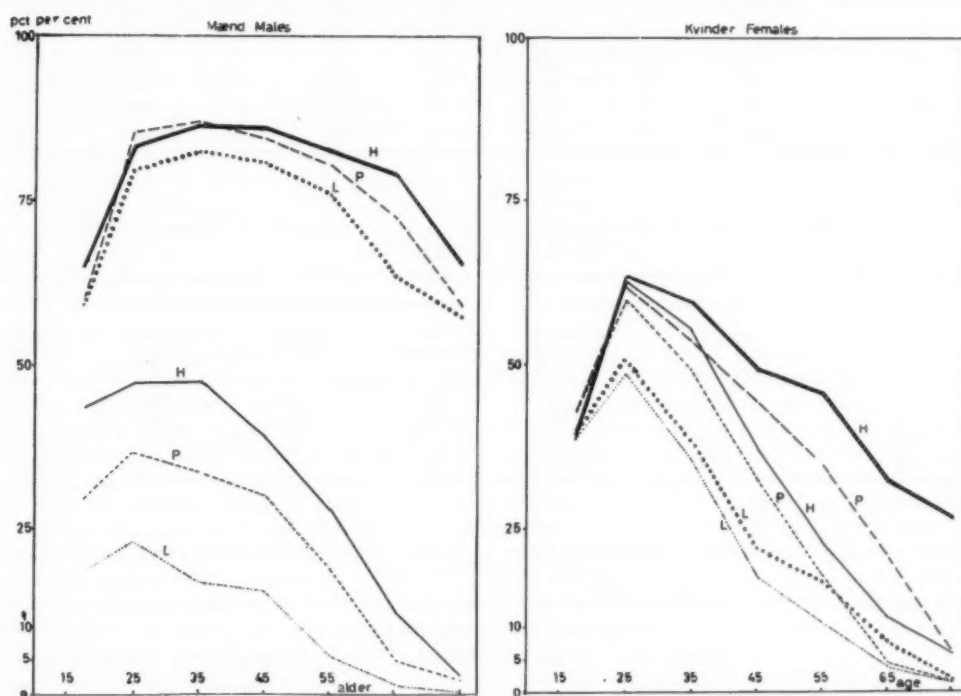


Fig. 11.

Smoking Habits in Denmark by Provinces in 1952—53 according to Sex and Age and Form of Tobacco.

cigaretrygere cigarette smokers	—	Hovedstaden H	—	alle andre rygere all other smokers
	- - - - -	Provinsbyer P	- - - - -	
	.....	Landdistrikter L	.....	
		Rural districts		

and cigarillo smokers, well aware of the impracticability of a complete distinction being made, in as much as in many cases the difference between the two forms of tobacco will be vague even to the smokers themselves. However, the geographical differences for both kinds are small

and can scarcely be credited with much importance.

Table 2 shows the age distribution of the various smokers in the same geographical sections. It is the young who smoke the cigarettes and, as is also shown in Fig. 11, the change-over to

Table 3.  
Male Smokers by Age, Form and Amount of Tobacco for each Province and all Denmark.  
August 1952 — April 1953.

Age	In per cent of all interviewed males: persons with a daily consumption of							
	less than 16 cigarettes	16 cigarettes a. o.	less than 26 g tobacco	26 g tobacco a. o.	less than 16 cigarettes	16 cigarettes a. o.	less than 26 g tobacco	26 g tobacco a. o.
	Whole country				Capital			
15—19 years	25.9	2.5	31.9	0.8	40.5	3.2	21.4	—
20—29 "	26.5	8.5	44.4	3.0	33.2	13.9	33.7	2.6
30—39 "	19.7	11.9	46.2	7.1	26.5	20.5	32.1	7.2
40—49 "	17.9	8.6	46.7	9.7	24.5	14.8	34.9	11.3
50—59 "	10.4	5.2	52.1	11.2	15.8	12.0	41.9	12.9
60—69 "	4.7	0.9	55.9	8.3	9.9	2.5	54.9	11.2
70 years and over	2.0	—	53.3	4.1	2.7	—	54.3	7.8
Total	16.6	6.8	47.4	7.0	23.7	12.7	37.3	7.8
	Provincial towns				Rural districts			
15—19 years	27.3	2.3	29.9	0.7	16.8	2.0	39.2	1.3
20—29 "	26.9	9.7	45.5	2.9	20.2	3.0	53.1	3.3
30—39 "	21.6	11.9	44.4	8.7	12.8	4.6	59.1	5.8
40—49 "	20.1	9.9	42.6	11.3	11.9	3.6	57.6	7.4
50—59 "	14.0	5.0	46.8	14.5	4.5	1.2	62.4	7.6
60—69 "	4.7	0.5	57.5	9.6	1.8	0.2	55.3	5.7
70 years and over	2.4	—	51.7	4.6	1.4	—	53.8	1.9
Total	18.1	7.2	45.4	8.4	10.5	2.4	55.8	5.3

Table 4.  
Female Smokers by Form of Tobacco for each Province and all Denmark.  
August 1952 — April 1953.

	Size of sample		In per cent of all interviewed females			
	total	of which smokers	all smokers	cigarette smokers	cigarillo smokers	pipe and cigar smokers
Capital	3,697	1,853	50.1	40.3	9.2	0.6
Provincial towns	3,928	1,702	43.3	35.4	6.8	1.2
Rural districts	4,175	1,151	27.6	24.0	2.6	1.0
Whole country	11,800	4,706	39.9	32.9	6.1	0.9

Table 5.  
Age Distribution of Female Smokers by Form of Tobacco for each Province and all Denmark.  
August 1952 — April 1953.

Age	In per cent of all interviewed females							
	Capital		Provincial towns		Rural districts		Whole country	
	Cigarettes	Other tobacco	Cigarettes	Other tobacco	Cigarettes	Other tobacco	Cigarettes	Other tobacco
15—19 years	39.2	0.8	42.6	0.4	38.3	1.5	40.0	1.0
20—29 "	62.7	0.6	59.5	1.8	48.4	2.3	57.3	1.6
30—39 "	55.3	3.5	49.3	4.5	35.7	2.9	46.8	3.7
40—49 "	37.2	11.8	32.4	12.1	18.3	3.9	28.7	9.0
50—59 "	22.8	22.8	18.3	16.2	10.8	6.3	16.8	14.4
60—69 "	12.2	19.8	4.9	16.3	2.9	5.3	6.4	13.1
70 years and over	6.4	20.3	1.5	4.4	0.3	1.7	2.3	7.7
Total	40.3	9.8	35.4	8.0	24.0	3.6	32.9	7.0

other forms of tobacco is only made at about the age of 40 — somewhat later in the towns than in the rural areas. After the age of 50 comes the heavy consumption of cigars or cigarillos; it holds good of males in all parts of the country

and presumably is connected not only with a change of taste but also with improved means. Another point is that the elderly are less accustomed to cigarettes from their young days, cigarette smoking having been anything but common in

Table 6.  
*Smokers Inhaling, by Sex and Form of Tobacco for each Province and all Denmark.*  
*January—April 1954.*

	Males				Females			
	Cigarette smokers		Other smokers		Cigarette smokers		Other smokers	
	total	of which inhaling per cent	total	of which inhaling per cent	total	of which inhaling per cent	total	of which inhaling per cent
Capital .....	522	86.4	722	43.4	640	69.7	179	5.0
Provincial towns ....	352	84.1	889	48.6	622	68.6	125	13.6
Rural districts .....	318	79.2	1,437	45.8	439	65.1	74	24.3
Whole country .....	1,192	83.8	3,048	46.0	1,701	68.1	378	11.6

Denmark before World War I. Pipe smokers seem to be the class least subject to a change of habit. In the rural areas many young men are also pipe smokers to compensate for the cigarettes which very probably are more difficult to smoke while working when employed in farming than in the urban occupations.

Cigarette smokers have been divided into two groups according to their consumption: those whose daily quantity does not exceed 15 cigarettes and those who smoke more, cf. Table 3. For the other classes of tobacco the boundary is placed at 25 g of tobacco, corresponding to an average of 6—7 cigarillos or 4 cigars.

From a health point of view the figures that are of most interest are the numbers of heavy smokers, a category which, as in Great Britain, comprises persons smoking at least 16 cigarettes a day, and as regards other tobaccos, 6 to 7 cigarillos or 4 cigars per day. Counting by this system of subdivision, 13 per cent of the adult male population of the capital are heavy cigarette smokers, compared with 7 per cent of the provincial towns and 2 per cent in the rural areas. In every case the number of heavy smokers is highest between the ages of 30 and 40, whereafter it declines, and among persons of over 60 years only about 1 per cent are heavy smokers.

With regard to smokers of other tobaccos the position is that the heavy smokers in the capital and the provincial towns represent about 8 per cent of them, against 5 per cent in the rural areas. Smokers of less than 26 g of tobacco daily in the capital reveal a steady increase with age, in direct contrast to smokers of fewer than 16 cigarettes daily. The same thing is found in the rural areas, but there the figures are not so regular as in the capital, and the change in the consumption according to age is less than in the capital.

Both size of consumption and contrast between the use of cigarettes and other tobaccos are most often greatest in the capital and lowest in the rural areas, the provincial towns midway between; the change in consumption is also most prominent among the population of the capital.

So far we have been dealing solely with male smokers, whose consumption is quite different

from that of females. Sixty per cent of adult females do not smoke at all, but among the 40 per cent of smokers there are marked differences between the three geographical regions, as will be seen from Table 4 and Figs. I and II. Half the women in the capital smoke, whereas among the rural population the figure is only one fourth. Once again the provincial towns lie midway between with just over two fifths. The women mainly smoke cigarettes, 33 per cent, 6 per cent smoking cigarillos and barely 1 per cent other tobaccos. As might have been expected, the age difference for female smokers is more pronounced than for males, the consumption of cigarettes being relatively very high among the young, i. e., persons of up to 40 years of age. Between 20 and 30 years two thirds of all women smoke cigarettes. This figure actually applies to the population of Copenhagen, but the curve describes more or less the same form, but on a lower level, in the provincial towns and the rural areas, see Table 5 and Fig. II. A large number of women of over 40 years smoke cigarillos, and between 50 and 60 years, at any rate in the capital, there is as much cigarillo smoking as cigarette smoking among women. When reaching 60 years and over, many more cigarillos than cigarettes are smoked everywhere, but the figures on which these calculations are based are not so large that too much significance can be credited to the various groups. But the tendency is unmistakable.

In the questionnaire employed for inquiring about the people's smoking habits (reproduced in the first article), one of the questions was: Do you inhale? Inhaling means drawing in the smoke so that it passes the lungs before being wholly or partly exhaled. The question of whether inhaling is inimical to health especially in conjunction with the topical problem of pulmonary cancer and tobacco, has not been clarified. The replies secured through the Morbidity Survey regarding inhaling must be viewed with reserve, partly because it is not all smokers who seem to understand the meaning of the word inhaling, and also because some evidently were ashamed to admit that they inhaled.

The chief result of the inquiry will be seen in Table 6 and Figs. III and IV, according to

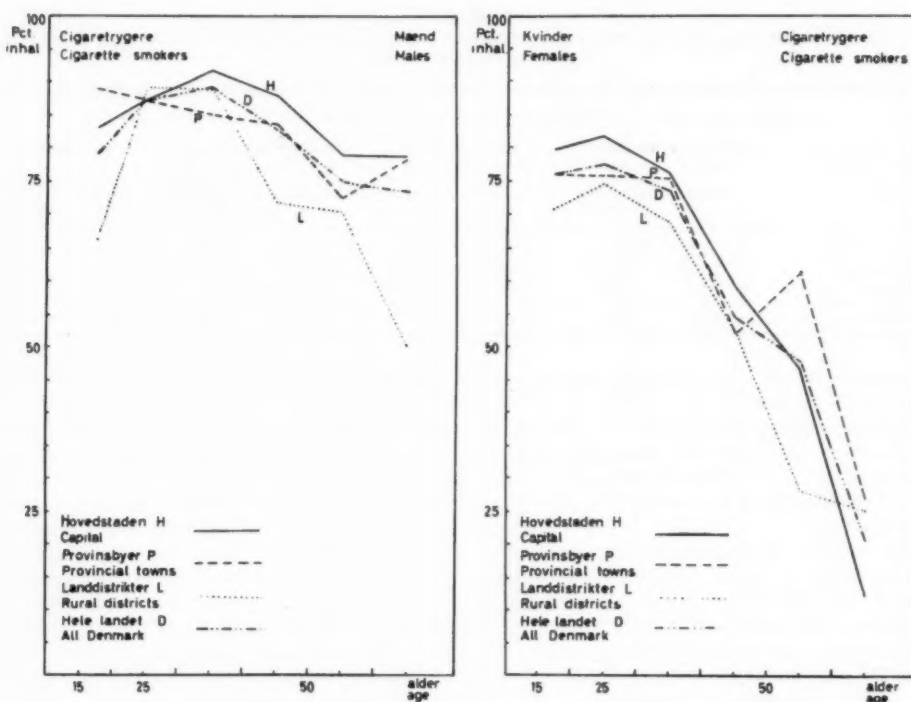


Fig. III.

Percentage of Inhaling Cigarette Smokers in Denmark by Provinces in 1954 according to Sex and Age.

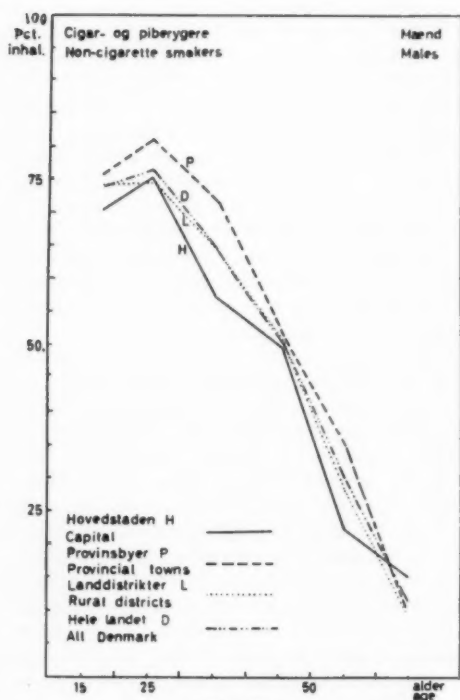


Fig. IV.

Percentage of Inhaling Male Non-cigarette Smokers in Denmark by Provinces in 1954 according to Age.

which cigarette smokers inhale more than other smokers. Next, males inhale much more than females — 84 per cent of all male cigarette smokers inhale, against 68 per cent of the females. Finally, the inhaling habit has a rather higher frequency in the capital and the provincial towns than in the rural areas, though the differences are not great. Of other smokers, barely half the males — presumably mostly pipe smokers — inhale against over 10 per cent of the females, as regards whom there is the curious fact that there is least inhaling in the capital and most in the rural areas.

Table 7 shows the percentage of inhaling smokers in different age groups. For cigarette smokers there is not much difference between the various age groups, which signifies that once a person begins to inhale he continues to do so. This applies only to the males, however, whereas the habit of inhaling among cigarette smoking women decreases with age. In the latter case it should be borne in mind that the number of women smokers in the higher ages is low and the figures more subject to chance fluctuations.

Men who smoke other tobacco than cigarettes inhale up to the age of 50, whereafter the habit falls off heavily, partly because it is cigar smoking which is most common in these age groups.

In connection with the inquiry into the consumption of tobacco in Denmark, there is the



Table 7.  
Percentage of Inhaling Smokers in each Age Group by Sex and Form of Tobacco for each Province and all Denmark.  
January—April 1954.

Age	Per cent of inhaling smokers													
	Capital		Provincial towns				Rural districts				Whole country			
	cigarette smokers		other smokers		cigarette smokers		other smokers		cigarette smokers		other smokers		cigarette smokers	
	males	females	males	females	males	females	males	females	males	females	males	females	males	females
15—19 years	82.9	79.7	70.0	88.9	75.7	75.7	65.8	70.8	74.0	79.1	75.7	73.6	(100.0)	
20—29 "	87.2	81.5	75.0	87.1	75.6	80.7	89.0	74.5	74.5	87.7	77.4	76.5	58.8	
30—39 "	92.0	76.2	57.2	84.9	75.2	71.1	88.6	68.8	64.0	88.8	73.5	64.5	33.3	
40—49 "	87.9	59.3	49.7	83.3	51.8	51.9	71.9	52.1	50.8	82.7	54.8	50.9	(8.1)	
50—59 "	78.6	46.6	22.3	72.2	61.0	34.8	70.3	(28.0)	28.3	74.8	47.6	29.0	(5.0)	
60—69 "	78.6	11.1	14.9	(77.8)	(26.7)	9.3	(50.0)	(25.0)	9.3	73.3	(19.5)	10.7	(3.6)	
70 years and over	(60.0)	—	(4.4)	...	...	(4.0)	...	...	(3.1)	(50.0)	...	(3.7)	(4.3)	
Total	86.4	69.7	43.4	84.1	68.6	48.6	72.2	65.1	45.8	83.8	68.1	46.0	11.6	

Numbers in brackets are based on less than 10 observations.  
... no smokers in this group.

Table 8.  
Age when Starting Smoking for Present and Former Smokers in all Denmark by Sex and Age in 1954.  
January—April 1954.

Age in 1954	Age when starting smoking. Per cent of interviewed										
	inter- viewed total	under 14 years	15—17 years	18—19 years	20—21 years	22—24 years	25—29 years	30—39 years	40—49 years	50 years and over	never smoked
<b>Males</b>											
15—19 years	462	26.6	35.2	2.3	.	.	.	.	.	.	35.9
20—29 "	921	20.2	44.3	17.0	4.7	1.6	0.2	.	.	.	12.1
30—39 "	1,147	17.8	40.9	18.4	7.6	3.2	1.8	0.5	.	.	9.8
40—49 "	1,076	17.3	38.4	17.6	8.5	2.6	1.8	2.8	0.4	.	10.6
50—59 "	830	20.9	32.2	15.3	12.1	3.1	2.7	2.6	1.4	.	9.6
60—69 "	606	18.4	32.1	16.1	9.9	2.7	2.5	2.7	1.3	.	14.4
70 years and over	411	16.2	26.9	14.4	12.1	2.3	1.7	1.7	1.7	.	22.9
<b>Females</b>											
15—19 years	494	7.1	34.4	2.8	.	.	.	.	.	.	55.7
20—29 "	1,021	2.8	23.0	23.5	12.9	3.9	1.6	.	.	.	32.2
30—39 "	1,088	2.0	10.9	14.0	14.2	6.1	10.2	6.4	.	.	36.2
40—49 "	989	1.5	4.7	5.7	10.7	3.9	5.9	17.0	5.4	.	45.0
50—59 "	790	1.7	2.6	3.5	5.4	2.2	5.0	10.1	13.2	2.0	54.2
60—69 "	525	0.7	2.5	1.4	6.0	1.1	4.6	6.4	7.5	9.2	60.6
70 years and over	366	1.6	2.4	1.6	6.4	—	1.6	4.0	2.4	8.0	71.9

question of the age at which people begin to smoke regularly. Information on this point too was procured through the Morbidity Survey questionnaire and it has led to the following result, see also Table 8 and Fig. V.

For the purpose of establishing the initial age of smokers, the investigation also included persons who once smoked regularly but ceased to do so later. In the first four months of 1954, 5,453 males were asked about their tobacco habits. 77.8 per cent of them were still smokers, 8.2 per cent had smoked earlier but gave it up, and 14 per cent had never smoked. The same question was put to 5,273 females, of whom 39.4 per cent were still smokers, 14.1 per cent had stopped the habit and 46.5 per cent had never smoked.

It now appears as regards the males that there have been no changes in their habit for many years. About 20 per cent of them have always begun to smoke before they were 15 years old. In the group between 15 and 18 years the percentage up to the last decades or so was 25 whereas it is now 40, which means a big growth in the number of smokers in these early years. Of males between 18 and 20 years, about 20 per cent began to smoke at these ages, so that there are now 80 per cent who smoked before they were 20 years old, compared with 65 per cent some years ago. Allowing the young men to become a year older, 21 years, the percentage of smokers becomes still higher than 80, in other words the difference between older and younger

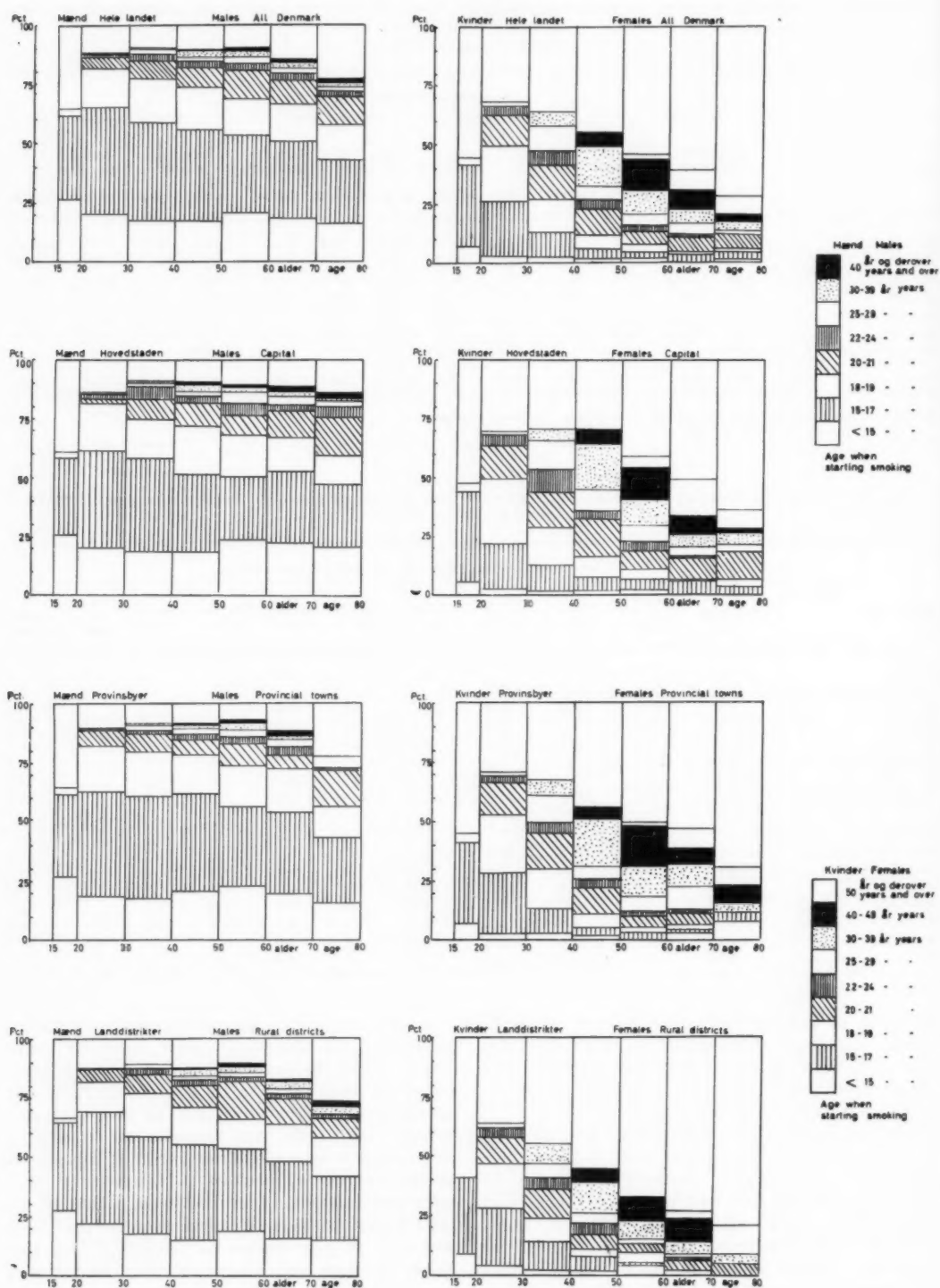


Fig. V.  
Smoking Habits in Denmark 1954 according to Age when Starting Smoking, by Provinces,  
Sex and Age in 1954. (Present and Former Smokers).

Table 9.  
Present and Former Smokers by Sex for each Province and all Denmark.  
January — April 1954.

	Size of sample	Males			Size of sample	Females		
		smokes now	smoked before	never smoked		smokes now	smoked before	never smoked
Capital .....	1,531	1,244	85	202	1,602	819	175	608
Provincial towns ....	1,571	1,241	131	199	1,717	747	223	747
Rural districts .....	2,351	1,755	233	363	1,954	513	344	1,097
Whole country total ..	5,453	4,240	449	764	5,273	2,079	742	2,452
Whole country per cent	100.0	77.8	8.2	14.0	100.0	39.4	14.1	46.5

generations becomes somewhat smaller, which may be due to the trick of the memory that the age of 21 is remembered better than that of 20, see Fig. VI. As 86 per cent of all adult Danish males admit to being or to having been regular smokers, it is clear that there are very few who begin to smoke after reaching 21, 10 per cent at most.

Within the various geographical areas there is not much difference between the initial smoking age of the males; the most marked change is to be seen in the rural areas where they now begin to smoke somewhat earlier than before.

As regards females, there are more perceptible changes between then and now, and also between the geographical areas. Very few women begin to smoke before they are 15, and until recently there were very few female smokers among those of 15 to 17 years. By the time they are 20, however, the great majority of women smokers have taken the step, i. e., 50 per cent of all females; going up to 21 years the percentage becomes 60.

In contrast to what was found for the men, however, there is a steady increase of smokers over the twentieth year too; no small number of

30, 40 and 50 year-old women began to smoke at these ages. This means that the great difference in the smoking habits of males and females will slowly diminish, because among the young there is not so much difference in the number of smokers. Taking the whole country together, 70 per cent of females under 30 years were or had been smokers, compared with 90 per cent of the males. Within the 3 areas the position is: in the capital 70 per cent of the women smoke right up to the age of 50, in the provincial towns up to 40 years, but in the rural areas only up to the 30th year. Thus the smoking habits of men and women are rapidly becoming the same.

In order to ascertain what effect it would have on the curves if those who used to smoke had continued to do so, we have added the number of those former smokers to those of the present smokers (*viz.*, Table 9) and plotted the curve in Fig. VI.

It will be seen that the curve for males becomes flatter, or, in other words, there is less difference between the generations. Accordingly, part of the difference observable on the general smoker curve is caused by those who gradually cease to smoke. The slight fall among the oldest is presumably a result of the fact that chewing tobacco and snuff were in wider use formerly than they are now. The curves for the different areas have also come closer together when the previous smokers are included.

For females the equalizing tendency between the generations is less obvious than for males, and it comprises only the youngest age-groups. Accordingly, this considerable difference between the female generations can only mean that more women smoke now than before, but this development began earlier in the capital than in the provincial towns, and there again earlier than in the rural areas. Among the women too the curves for the present + former smokers describe a more similar course than for the present smokers alone — a difference that is greatest in the rural areas, whether the cause be that many women in the rural areas really smoke only a short time and then give the habit up — at any rate regular smoking — or whether they are less disposed to

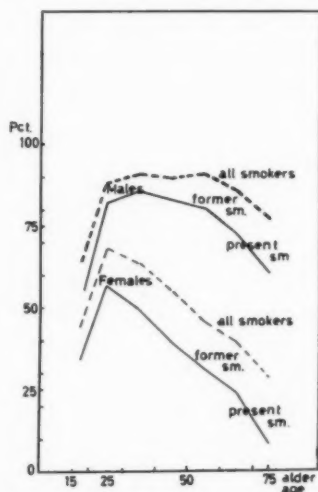


Fig. VI.  
Percentage of Present and Former Smokers  
in all Denmark 1954 by Sex and Age.

admit that they smoke now, whereas they do not mind saying that they once smoked tobacco.

#### SUMMARY

"Tobacco Consumption in Denmark" I and II concerns the consumption of the various forms of tobacco, compiled from replies received from a representative selection of adult persons in two periods of the Morbidity Survey. In August 1952—April 1953 questions were put to 23,000 people, and in January—April 1954 to 11,000. The general result of these inquiries is as follows:

78 per cent of all adult males are smokers; 8 per cent have smoked previously and 14 per cent have never smoked. For females the corresponding figures are 40, 14 and 46 per cent. Of the 78 per cent male smokers, 24 per cent smoke cigarettes, 38 per cent pipes, 9 per cent cigarillos and 7 per cent cigars. Among the females, 33 per cent are cigarette smokers whereas 6 per cent smoke cigarillos and fewer than 1 per cent cigars or pipes.

The number of smokers varies with age and for males is highest at the age of 35, for females at 25 years; after that there is a slight decrease for males and a heavier decrease for females; males of over 70 years are as numerous as males of under 20, but females of over 70 years rarely smoke.

In the metropolitan area, 82 per cent of the males were smokers, in the provinces 79 and in the rural areas 74 per cent. For females the percentages were 50, 43 and 28 per cent, respectively.

Out in the country the men mostly smoke pipes, 45 per cent against 29 per cent for all other forms of smoking; in the capital it is mostly cigarettes, by males 36 per cent against 29 per cent pipe tobacco and 16 per cent cigars and cigarillos. In all areas women mostly smoke cigarettes.

The habits vary with age: younger males smoke cigarettes and elderly males cigars, whereas pipe smoking is about the same in all age groups. Among the women too it is the younger ones who smoke cigarettes, the older women preferring cigarillos. 14 per cent of the males and 1 per cent of the females may be characterized as heavy smokers, their daily consumption being more than 15 cigarettes or the corresponding quantities of other tobacco.

Inhaling was found to be a habit among 84 per cent of the male cigarette smokers and 68 per cent of the females. Among smokers of other tobacco, 46 per cent of the males inhale and 12 per cent of the females.

In all parts of the country, 20 per cent of the males begin to smoke before they are 15 years old and 80 per cent before they are 21. In the age group 15—21 smoking now begins somewhat earlier than previously.

Very few females smoke before they are 15, whereas 60 per cent are smokers before reaching the age of 21. Smoking begins earliest in the capital and latest in the rural areas, and everywhere rather earlier now than before. In contrast to what is the case with males, many women do not begin to smoke until after the age of 21.



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